Universidade de Aveiro
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Secção Autónoma de Ciências da Saúde

Cálida Etezana Rodrigues da Veiga

Relatório de estágio curricular na ARFA.

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Relatório de estágio curricular ARFA.

Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Biomedicina Farmacêutica, realizada sob a orientação científica do Dr. Eduardo Tavares, Diretor da Direção de Regulação Farmacêutica da Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares e da Professora Doutora Maria Teresa Herdeiro, Professora Auxiliar Convidada da Secção Autónoma de Ciências da Saúde da Universidade de Aveiro.

Dedico este trabalho aos meus pais pelo incansável apoio.

O júri

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palavras-chave

Ciências Biomédicas, Biomedicina Farmacêutica, Farmacovigilância, reação adversa medicamentosa, notificação espontânea, Autoridade Reguladora Nacional de Medicamentos, Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares

resumo

O presente relatório visa apresentar as atividades desenvolvidas durante um estágio curricular de 9 meses na Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares (ARFA).
O objectivo deste estágio na Direção de Regulação Farmacêutica da ARFA foi colocar em prática os conhecimentos e competências adquiridas durante o primeiro ano do mestrado. A gestão do projeto do Sistema Nacional de Farmacovigilância foi uma das principais atividades desenvolvidas durante o estágio. Ademais, tive a oportunidade de experimentar outras áreas de intervenção da agência, que foram também bastante enriquecedoras. Este estágio proporcionou uma visão clara e abrangente de como funciona o sector farmacêutico em Cabo Verde, bem como das limitações da farmacovigilância em países em desenvolvimento, como o caso de Cabo Verde.

keywords

Biomedical Science, Pharmaceutical Biomedicine, Pharmacovigilance, adverse drug reactions, spontaenous reporting, National Medicine Regulatory Authority, Agency for Regulation and Supervision of Drugs and Foodstuffs (ARFA)

abstract

This report intends to present the activities developed during 9-month internship at the Agency for Regulation and Supervision of Pharmaceuticals and Food (ARFA). The objective of the internship at the Direction of Pharmaceutical Regulation of ARFA was to put into practice the knowledge and skills acquired during the first year of the masters'degree. The management of the project of the National Pharmacovigilance System was one of the main activity developed in the direction. Moreover, the opportunity to experience other area of the agency was possible and equally enriching. This internship provided a clear and comprehensive view of how the pharmaceutical sector works in Cape Verde, as well as the limitations of pharmacovigilance in developing countries, as the case of Cape Verde.

Table of Contents

Figure and Tables Index

Abbreviation

ACTs	Artemisinin-based Combination Therapy
ADR	Adverse Drug Reaction
ARFA	Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares *(Agency for Regulation and Supervision of Drugs and Foodstuffs)*
ARVs	Antiretroviral
CNEPS	Comissão Nacional de Ética Para Investigação em Saúde Pública *(National Ethics Committee for Health Research)*
DGFM	Direção Geral da Farmácia e do Medicamento *(General Directorate of Pharmacy)*
DL	Decree-Law
DPR	Directorate of Pharmaceutical Regulation
EMPROFAC	Empresa Nacional de Produtos Farmacêuticos, S.A.R.L;
E2B	Efficacy Topics' Data Elements for Transmission of Adverse Drug Reactions Reports (ICH)
HIV/AIDS	Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome
i.e.	id est
ICSR	Individual Case reports of Suspected Adverse Drug
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
e.g.	exempli gratia
INHARMA	Indústria Farmacêutica, S.A.R.L.;
INN	International Non-proprietary Name
INPS	Instituto Nacional de Previdência Social
MedDRA	Medical Dictionary for Regulatory Activities
MAH	Marketing Authorization Holder
MPP	Maximum Price to Pharmacy
NML	National Medicine List
NHS	National Health System
NPP	National Pharmaceutical Policy
NMRA	National Medicine Regulatory Authority
MPC	Maximum Price to the consumer
RMP	Risk Management Plan
SIMFAR	Sistema Integrado de Monitorização do Mercado Farmacêutico
SPC	Summary of Product Characteristic
SPW	Sale Price to Wholesaler
UMC	Uppsala Monitoring Centre
USA	United States of America
WHO	World Health Organization
WHO-ART	WHO Adverse Reactions Terminology

Introduction

Within the scope of the Master in Pharmaceutical Biomedicine, I enrolled in an internship from September 2012 to June 2013. This internship was held in the pharmaceutical directorate of ARFA, in Cape Verde, during the second year of my master degree.

The main purpose was to allow a closed contact with pharmaceutical environment in order to apply and complement the theoretical background attained during the first year of my master degree; to gain practical knowledge through the application of the attained skills and with the experience of senior professionals and to understand the multidisciplinary framework of a national medicines regulatory authority (NMRA), especially at the pharmacovigilance field.

The first weeks of the curricular training comprised the basic introduction to ARFA in terms of how it is organized, applicable laws and its main role in the pharmaceutical environment.

The internship was then divided in two main components:

- Permanent Management of the pharmacovigilance system;
- Training and experimentation of other areas of the agency;

This report describes my working experience during the internship, starting by providing the general knowledge associated to pharmacovigilance and characterizing ARFA and its role in the pharmaceutical environment in Cape Verde, and also by reporting all activities performed there. So, it is divided in 5 chapters, defined as:

- State of the art: this chapter starts by providing the general knowledge associated to pharmacovigilance and also the current state of the pharmacovigilance in Africa.
- Host Organization Characterization: this chapter starts by providing a brief overview of the health and the pharmaceutical environment in Cape Verde, followed by a portrayal of the host organization.
- Activities Description: this chapter describes the main and the multidisciplinary activities performed at ARFA.
- Discussion: this chapter discusses the main gains achieved during this internship, the main difficulties encountered, as well as the general limitation of pharmacovigilance in Cape Verde.
- Conclusion: this chapter gives an overview of my internship experience highlighting the importance of strengthening pharmacovigilance in Cape Verde.

1. State of art

Over the past few years, medicines have changed the way in which diseases are managed and controlled and, the world has achieved major progresses in their health status(1). The increase in the worldwide life expectancy and the improvement in the quality of life of many people by preventing diseases, reducing disability and slowing disease progression are some of the benefits achieved with medicines(2). However, despite these positive effects, medicines are not free of risks and harmful effects resulting from their use are also known to be as old as medicine itself. Nonetheless, the medicine safety issue was not the primary concern in their use(3).

The history of pharmacovigilance goes back as much as fifty years ago, and the worldwide mark was the thalidomide tragedy in 1961-1962. Thalidomide was approved in 1957 as a safe and effective hypnotic and anti-emetic, and quickly became the most popular medicine to treat nausea and vomiting in early pregnancy. Terribly, few years later this medicine proved to be a potent human teratogen by causing phocomelia in approximately 10.000 children in countries in which it was broadly used(3-5).

To address this worldwide tragedy, the World Health Organization (WHO) was requested to take an active role in assuring the safety of medicines and, it was in 1963 during the 16th WHO General Assembly that the pharmacovigilance was officially created. This science or activity is associated to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem(3, 4). Thalidomide was withdrawn from the market in 1965 however is still used today to treat a wide range of medical conditions such as the multiple myeloma, multiple sclerosis and Crohn's disease(3).

This disaster made the world to realize that the medicine's safety is as well important as its efficacy and, in 1978 the safety issues related to medicines was then globalized, strengthened and systematized with the establishment of the WHO programme for international drug monitoring(6, 7). The Uppsala Monitoring Centre (UMC) is responsible for managing this international programme through the collection, storage and analysis of individual case reports of suspected ADR (ICSR) submitted by the National Centres. Currently approximately 110 countries make part of this programme as official member countries and 33 countries as associate members, including developed, developing and under-developed countries(8).

This need to collect the safety information of medicines during its post-authorization phase is mainly because the safety data generated during the clinical trials are not enough to

map out all possible adverse effects due to the limitations of the studies such as the(9, 10):

- Limited size (no more than 5000 and often as little as 500 volunteers is used which is insufficient for the detection of rare adverse effect);
- Strict eligibility criteria (exclusion of concomitant therapies and diseases);
- Narrow indications (only the specific disease is studied);
- Short duration (often no longer than a few weeks);

Thus, despite the concept of adverse drug reaction (ADR) is not standardized, the WHO's definition of ADR has been in use for about 30 years, and it widely accepted as "*a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function*" (11). In Europe, this concept was adapted last year to include noxious and unintended responses that resulted from the use of medicine within and outside the terms of the marketing authorization thus including, medication error, misuse, abuse and occupational exposure(12).

ADR is a cross-cutting problem that affects children, teen, adult and seniors. Nevertheless the elderly population is considered a special case, since the majorities of them are polimedicated and have concurrent medical illnesses, alterations in pharmacokinetic and pharmacodynamic parameters(13). Furthermore, polypharmacy can exponentially increase the rate of ADRs because patients in 4 or more medications have an increased likelihood of drug interactions(14).

Thus, considered today as a challenge issue in the healthcare, ADRs are deemed to be responsible for 3–7% of all hospitalizations and affecting 10-20% of all hospitalized patients(13, 15). Besides, although over 70% of all ADRs are potentially preventable, the mortality and morbidity associated to the consumption of medicines represents a serious health problem(13). For example, in the USA ADRs are assigned to be responsible for about 106.000 deaths per year and are among the six leading causes of death ahead of diabetes and traffic accidents(14). In Europe the scenario is not different and ADRs are responsible for approximately 197.000 deaths per year(12).

Hence, based on this fact ADRs are considered to be a major cause of morbidity and mortality in health care. Moreover, ADRs may have a significant impact in the health budget especially when both cause or extend hospitalization. The cost associated to ADRs is estimated by the increasing in the length of hospitalization because the direct and indirect costs resulting from ADRs are difficult to estimate(13).

In general, ADRs in hospitalized patient may increase the length of hospitalization from 2-4 days, which may represent an additional cost of approximately $2500 per patient. In some countries this increase in the length of hospitalization may represent an increase of 15-20% of their healthcare budget(8, 16). For example, in the USA the estimated cost of drug-related morbidity and mortality is approximately $136 billion annually, which is more than the total cost of cardiovascular or diabetic care. In Europe the total cost associated to ADRs is approximately €79 billion annually(12, 14).

This scenario allows classifying the iatrogenic drug disease as frequent, serious and troublingly by its cross-cutting impact on health and economy. So, the pharmacovigilance can represent an important tool to continuously assure a positive balance between the risk and benefit of medicines and reduce or minimize the cost of ADRs.

Therefore, to enhance the likelihood of detecting ADRs before and after the medicines authorization, pharmacovigilance uses a wide range of tools and processes. The spontaneous report and the case reports/ case series are one of the main tools used in pharmacovigilance to generate hypothesis, which will later be confirmed through epidemiological studies such as cohort/case-control studies and randomized controlled trials. In addition, some countries like the United Kingdom and the New Zealand combine aspects of spontaneous report with epidemiological studies to generate-confirm hypothesis through the prescription event monitoring. Nevertheless, the spontaneous report is most widely used in the active surveillance of medicines(3).

1.1 Pharmacovigilance in Africa

Over the past 10 years pharmacovigilance has seen tremendous growth, and in Africa, for example, the number of countries with “good” pharmacovigilance capacity increased from 5 in 2000 to 23 by the end of 2010. Nevertheless, different reasons and needs have conducted the development of pharmacovigilance in different parts of the world. In developing countries for example, resource constraints and disease demographics, particularly the focus on HIV/AIDS, malaria and tuberculosis, have influenced the growth of pharmacovigilance, while demand for greater transparency, accountability and access to information has driven pharmacovigilance in the developed world(7).

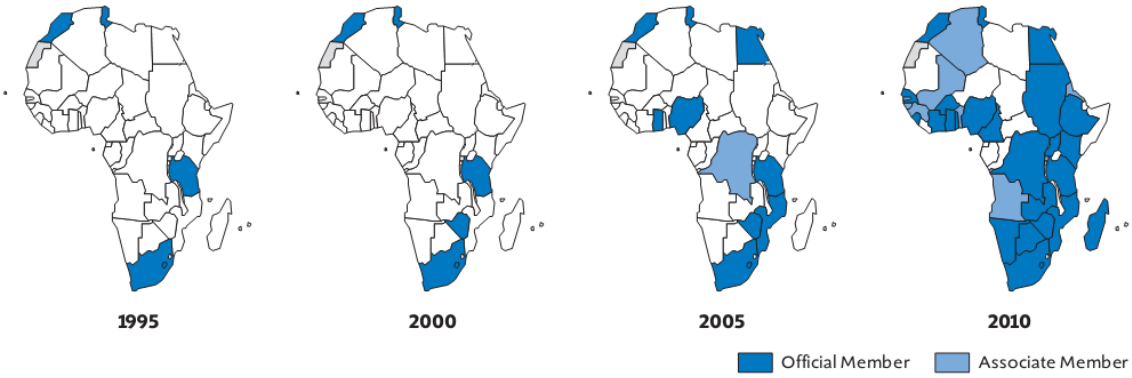

Figure 1: Growth of pharmacovigilance in Africa in 15 years (1995-2010)

Consequently, with increasing access to essential medicines newly introduced as the combination therapy of artemisinin-based (ACTs) and antiretrovirals (ARVs), the importance of surveillance of drug-related problems, particularly in Africa where vulnerable populations are receiving treatment for HIV/AIDS, Tuberculosis and malaria, is becoming increasingly evident(17). Currently approximately 31 African countries are official members of the WHO-UMC Program and 8 countries are associate members(18).

This awareness, together with the emphasis on global cooperation, helps to strengthening the safety of medicines even in resource-limited countries. However, a study in 55 low- and middle-income countries demonstrated that there are important characteristics and gaps in those national pharmacovigilance centres in African that can compromise the safety monitoring and evaluation of medicines. One of the main features is that most of the centres are severely understaffed (2 to 4 staffs) and under-resourced(19). This framework is also present in Cape Verde.

Regarding the impact of ADRs on patient morbidity and hospitalization in Africa, several studies have documented, and it is estimated that 4.5 to 8.4 percent of all hospital admissions in Africa are related to ADRs, and that 6,3 - 49.5 percent of all hospitalized patients develop ADRs(20, 21). Furthermore, it is estimated that 45.5 percent of the modification or interruptions in antiretroviral therapy are due to the ADRs. For example, HIV-infected patients receiving antiretroviral therapy were more likely to be admitted with an ADR than those who are not on antiretroviral therapy (20).

Therefore, besides the impact of ADRs on morbidity and mortality and the attendant costs to health systems, ADRs also have other associated costs in terms of the loss of confidence in the health system, economic loss to the pharmaceutical industry, non-adherence to treatment, and development of drug resistance. The importance of pharmacovigilance in African countries and other countries is that, regardless the

existence of pharmacovigilance system, ADRs continue to occurring however when pharmacovigilance system does not exist at all, the size and magnitude of the problem are completely unknown. For example, inappropriate uses of medicines abound, preventable ADRs occur, cost of health care delivery escalates, unsafe and poor-quality products in the supply chain goes completely undetected, and harm or even death can occur from use of poor-quality products(17).

In African and other region of globe spontaneous reporting is the rule. However, currently there is a growing interest in Africa to introduce active surveillance of cohorts of patients in specific disease programmes, as with Cohort Event Monitoring (CEM). For example, there is two programmes, supported by WHO, already under way for ACTs in Nigeria and the United Republic of Tanzania(22).

2. Host organization characterization

This chapter describes the pharmaceutical sector in Cape Verde, the host company, its purpose and activities.

2.1 Overview of Health System in Cape Verde

Cape Verde is an archipelago of volcanic origin located on the West African coast, compound by 10th islands: Santo Antao, S. Vicente, Santa Luzia, S. Nicolau, Sal, Boa Vista; May; Santiago, Fogo and Brava. The archipelago has about 491,875 inhabitants, according to the census taken in 2010, of which 50.5% are women. Praia is the capital with 1301.602 inhabitants, and is the country's largest city(7).

In relation to the health system organization, in Cape Verde the National Health System is designed to include all public and private entities for quality control, research, import, production and marketing of medicines and other products used to provide healthcare. At the central level, the system includes the departments and agencies that assist the Minister in the formulation of health policy, in the exercise of regulatory functions of the system and the evaluation of its performance. The decentralization of the national health system is made through the delegacies of health whose district coincides with the county or municipality (the basis of the administrative division of the country)(23).

On providers of health care, the country has two central hospitals, three regional hospitals, twenty two health centers, thirty-four health centers, one hundred and seventeen basic health units, five centers of reproductive health centers and two mental health centers. It should be noted that reproductive health care is provided to all health centers. Regarding human resources, in 2011, the physician ratio was 5.7 / 10,000 inhabitants, 10.4 / 10,000 inhabitants for nurses ratio and 0.4 /10,000 inhabitants for pharmacists ratio(24).

The country is in the transitional phase of the epidemiological profile, where noncommunicable disease have been overcome in terms of prevalence and severity communicable disease, although acute respiratory infections diseases, diarrheal, tuberculosis and HIV/AIDS infection continue to represent a public health problem.

The average life expectancy at birth in the country, estimated in 2013, is 71.28 years, and 66 years for hoemens and 71 years for women. In 2013, the estimated mortality rate is around 6.22 deaths/1.000 inhabitants, and the birth rate around 20.96 births /1.000 inhabitants(25).

2.2 Overview of Pharmaceutical Sector in Cape Verde

The global pharmaceutical environment is undergoing multiple changes at different level, with the emergence of new paradigms in the areas of manufacture and treatment, particularly with a focus on personalized medicine and advanced therapies. Thus, in this global frame, challenges increasingly larger and more complex arise to the NMRA, requiring new regulations, guidelines and laws regarding the safety, quality and efficacy of new medicinal products.

In Cape Verde the regulation of the exercise of pharmaceutical activity is installed and develops with progression at efficacy and credibility level. From its impact on the public heath arise already substantial and evident gains, announcing a future of greater solidity and balance of interest to all of those involved. The characteristics of the sector in Cape Verde are typical of a market in which parts of the chain are in monopoly, controlled by agreements, formal and informal, as regards the form of activities of agents in the market. The main players in the value chain are the suppliers, producers, wholesalers and retailers.

With regard to the regulatory bodies, it should be noted that the following main entities are involved: the General Directorate of Pharmacy (DGFM) and the Agency for Regulation and Supervision of Drugs and Foodstuffs (ARFA).

The DGFM is a central service of the health minister whose mission is to define, regulate, implement and evaluate the National Pharmaceutical Policy (NPP) for the protection of public health and assurance of access of health professionals and citizens to medicines and health products of quality, safe and effectives. The DGFM is also responsible to coordinate and provide technical support to the management of medical devices. Thus, among other aspects, the DGFM is responsible to(26):

- Promote and participate in policy formulation on the production, marketing, import, export, re-export control and consumption of medicines and other pharmaceutical products;
- Organize competitions and license industrial and commercial establishments that manufacture and marketing medicines and supplies;
- Maintain update the records of pharmacies, manufacturer, warehouses and the National Medicines List (NML);
- Contribute to the quality assurance of medicines;

With the recent approval of the decree-law which establishes the new status of ARFA, the competence of DGFM of marketing authorization of medicines, distribution and monitoring was revoked, being now, the ARFA the responsible for this competency(27).

The ARFA is responsible for the exercise of administrative activity of technical and economic regulation of the pharmaceutical sector and food. In terms of pharmaceutical regulation, the ARFA is responsible for medicine marketing authorization and monitoring (competences recently acquired), pricing and stock supervision. These competences will be further developed in the next section(27).

To understand the main agents of the pharmaceutical sector in Cape Verde, it is important to primarily understand that the choice of medicines to be imported meets a legal criteria, which establish that the International Non-proprietary Name (INN) to be imported must belong to the NML in force. Nevertheless, in situations duly provided by law (clinical conditions, investigations and clinical trials) medicines can be imported even if the INN does not belong to NML in force(28). The NML is the relationship of medicines whose market availability is guaranteed by the government, producers and importers(29). The update of the NML is ensured by the National Commission of Medicines, an advisory body whose members are appointed by the Minister of Health and formalized by publication in the Official Gazette. This commission is composed of physicians and pharmacists, representing the various players in the sector(26).

In terms of market operators it should be noted that the following entities are involved:

- EMPROFAC - Empresa Nacional de Produtos Farmacêuticos, S.A.R.L.;

Founded in 1979 as a public company, the EMPROFAC has to date a monopoly on the import and wholesale distribution of medicines. In 1997 became an anonymous society with the status of private company with 100 percent public capital. The EMPROFAC has as mission ensuring a regular supply of safe, effective, quality medicines. Currently 65% of medicines consumed in the country are imported by EMPROFAC, and the remaining acquired through the INPHARMA(30).

The INN imported by the EMPROFAC must belong to the NML. The purchase of pharmaceutical product is done by two methods: 1) annual procurement through international competition for products intended to hospital facilities; and 2) Direct procurement through suppliers of recognized quality. The requests are made annually with the indicative quantities and orders and are made four times a year, which allows to adjust the quantities to the current consumption(31).

- INPHARMA - Indústria Farmacêutica, S.A.R.L.;

The INPHARMA is a Portuguese-Cape Verdean company under private law, created with the objective of strengthening the autonomy of the country in the pharmaceutical sector; reduce foreign exchange costs; capture technologies and to value the existing human resources through the creation of jobs. The INPHARMA covers approximately 36% of domestic consumption. The production of medicines is based on generic and brand medicines manufacturing under license of other partners (eg. Labesfal and Azevedos). Injectable products are not manufactured by require high investments. Besides, due to the limitation of the internal market, production is usually limited to products most consumed medicines in the country(32). The share of INPHARMA in the medicinal product market has grown while remaining at around 36%, mainly due to the model of the pharmaceutical sector in Cape Verde. The non-privatization of EMPROFAC, which holds 40% of INPHARMA, has been one of the major constraint to the INPHARMA(33).

In relation to the distribution of the imported products, the private sector is supplied directly by the EMPROFAC and accounts for about 60% of the distribution. The public sector (health centers) is supplied through the deposits of DGFM: Central (Praia) and Regional (Mindelo), who acquire products from the EMPROFAC and INPHARMA. Given the autonomy provided to the Central Hospitals ("Agostinho Neto" (Praia) and "Baptista de Sousa" (Mindelo)) these facilities can be directly supplied by the EMPROFAC and INPHARMA(34)."

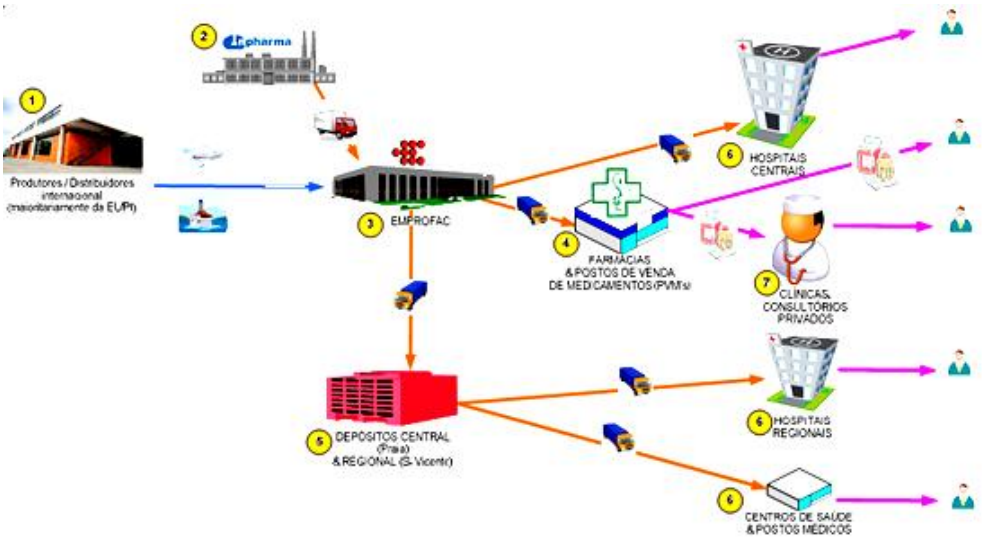

Figure 2: Pharmaceutical Sector in Cape Verde

To understand the pricing system in force in Cape Verde, it is important to emphasize that all medicines imported are pre-selected based on INN. In Cape Verde, are subject to the

pricing system all existing medicines in the country, with the exception of non-prescription medicines, herbal remedies, homeopathic, manipulated and veterinary medicines. The medicines excluded from the pricing system are, however, subject to monitoring procedures and regulation to be prepared by ARFA(35).

The medicines are supported by the National Institute of Social Security (INPS), Government Budget/Ministry of Health and by consumers. The INPS manages the reimbursement system, which covers approximately 25% of the population(34).

Although the pharmaceutical sector in Cape Verde has undergone major changes in its organization and functioning, limited human and financial resources did not allow a full evaluation of the medicinal product, mostly imported. The inequality in accessibility to medicines is deep, when comparing the situation of the beneficiaries of the INPS with a large proportion of the population who do not have the resources to health care expenses. All this factors encourages the unregulated supply chain such, street vendors and other unlicensed outlet, which may constitute a serious public health problem.

Furthermore, the limitations in the control system of imported products, which is restricted to the WHO certification and certificates of analysis provided by the supplier, and the inoperability of the Official Laboratory for Quality Control, only contribute to aggravate this scenario. Besides, the inspective ability is also manifestly weak due to lack of technical and financial resources.

2.3 Overview of the Host Organization

My internship occurred at ARFA, a NMRA, which is situated in Praia, the capital of Cape Verde. The ARFA was established in 2004 by Decree-Law (DL) nº 42/2004 of 18 October 2004 to carry out technical and economic regulation of food and pharmaceutical products. The ARFA's mission is to ensure that the population of Cape Verde has access to medicines and foods of quality and safe. The ARFA still has the mission to follow the market supply of staple foods, especially in proceedings relating to food aid. (36).

Thus, under the program "State Reform and Public Administration", which aims at strengthening citizenship, modernization, transparency and rationalization of structures, was recently approved the DL nº 22/2013 of 31 May 2013, which determines the incorporation of ARFA with the National Agency for Food Safety (ANSA), by the transferring the whole of the duties, powers and legal status, rights and obligations of ANSA to ARFA, and approves the new statutes of ARFA.

The ARFA while independent administrative authority, institutionally based, endowed with regulatory functions, including regulation, supervision, pricing and sanctioning of violations

enjoys administrative, financial and patrimonial autonomy. The ARFA, in its mission to defend the legitimate interests of consumers has in particular the following pharmaceutical competencies(27):

a) Regulation Competences

- Regulate and supervise activities related to the life cycle of pharmaceuticals products and food, aimed at sanitary food safety and quality and the safety and efficacy of pharmaceutical products;
- Regulate the functioning of the national pharmacovigilance system (NPS);
- Regulate technical requirements applied to production, import, export, distribution to ensure food safety and quality, safety, quality and efficacy of pharmaceutical products;
- Establish codes of good practice within their assignments, etc;

b) Supervision Competences

- Oversee the implementation and enforcement of laws, rules and technical requirements for regulated industries as well as the provisions of the respective titles of exercise activity;
- Ensure proper functioning of the market and its transparency, while respecting the established rules and standards, avoiding any practice that inhibits competition and harmful to the consumers, without prejudice to the powers of the competition authority;
- Supervision of the national supply of medicines subject to the regime of mandatory minimum stock as well as staple foods;
- Ensure and monitor the fulfilment of international obligations under its powers;

c) Pricing Competences

- Promote the establishment of mechanisms of control and price fixing of medicines and the supervision of its compliance;

d) Sanctioning Competences

- Prosecute and punish the violations to the laws and administrative regulations which it is responsible for implementation and supervision;
- Collaborate with external supervisory bodies of the state in initiation and prosecution of breach proceedings;

Thus, despite the vast body of powers conferred to ARFA, the agency's intervention does not include veterinary medicines and medical devices(27).

In organizational terms, the option for this stage favours a structure that is feasible, in light of human and financial conditioning that the agency can mobilize (Figure 1). However, the adopted structure is based on an evolutionary perspective, able to support developments that accumulated experience and external environment may justify. So with the recent merger of the agency, the organizational structure approved integrates:

- Bodies of the direction, supervision and consultation
- Technical Service

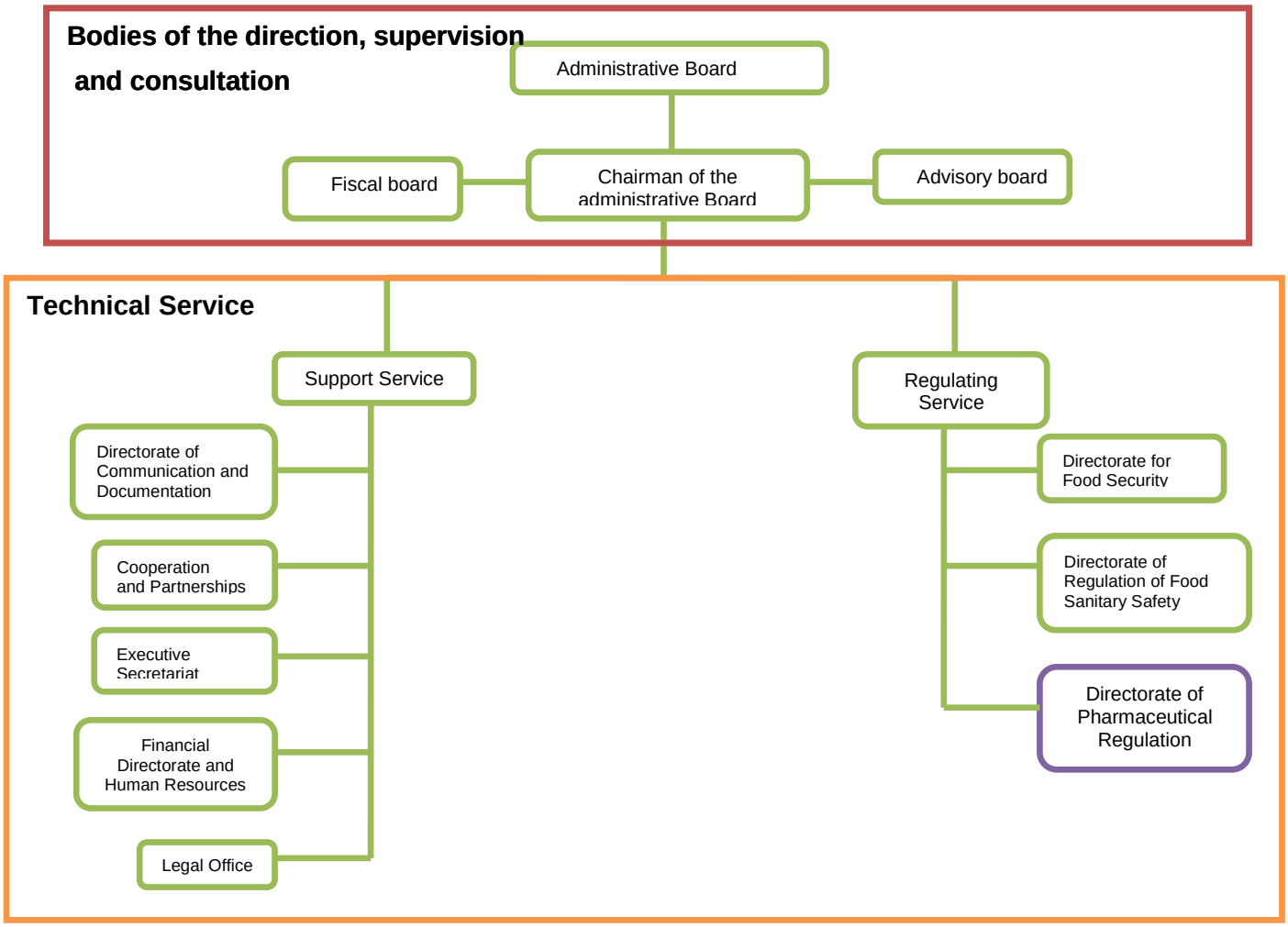

Figure 3: ARFA Organigram

To make effective the security in the consumption of pharmaceuticals and foodstuffs, the ARFA dispose not only of legal instruments, but also operational tools. Among the operational instruments stand out: the Integrated System of Monitoring of Pharmaceutical

Market (SIMFAR), with the configuration of a market observatory, which integrates economic regulation (drug stock /prices) and the drug post-marketing surveillance system (VIGIMED); the Food control System (SNCA) and the Integrated Rapid Alert System of Food (SIARA), configured for the detection of non-compliance situations inherent to foods that will reduce the risks associated with the consumption of food for human and animal consumption(37-39).

2.3.1 Directorate of Pharmaceutical Regulation

My internship occurred mainly at the directorate of pharmaceutical regulation (DPR) of ARFA. The DPR is the technical direction of the agency, which is responsible for technical and economic regulation of the pharmaceutical market, in order to promote the quality and safety to the consumers through the regulation and supervision of the activities related to the life cycle of pharmaceuticals products(36).

The responsibility of DPR can be divided in the three main areas of interventions and comprise the following competences:

- **Regulatory Framework**
  - Promote and coordinate the activities of standardization and harmonization of concepts, definitions and terminologies related to medicines, cosmetics and biocides;
  - Develop and propose draft laws, regulations, standards and requirements regarding:
    - The functioning of the national pharmacovigilance;
    - Pricing regime of medicines for human use;
    - Supply and stock management of medicines;
    - Production, import, export, distribution and advertising of medicines for human use;
    - Technical requirement to cosmetic products and biocides;

- **Technical and Economic Evaluation**
  - Manage the procedures and activities to ensure quality assurance, safety and efficacy required for marketing authorization of medicinal products for human use, cosmetics and biocides;

- Investigate the impact of international alerts on the national territory and propose safety measures;

- **Supervision and Market Monitoring**
  - Monitor the prices of medicines for human use, and evolution trend of medicines market;
  - Monitor the supply and distribution circuit of medicines for human use;
  - Ensure the collection and processing of information on the use of medicines;
  - Ensure the collection of statistical and economic data relating to the medicine sector;

The DRP is headed by the pharmacist, Dr. Eduardo Tavares, who is supported by other pharmacists and administrative staff. The direction is constituted by three multifunctional technicians. Thus, due to the limited human resources it is important that all directorate's members communicate effectively one with another and work together to maintain the agency scientific standards. To facilitate this, all members of the directorate meet on a monthly basis to keep one another's updated on their main activities, new activities assignments or other recent important scheduled events.

The DRP is also responsible for the preparation and communication of any safety alert with medicines to the health professionals and market operators. Recently, I was responsible to the development of one of the ARFA's publications: the *"Obseratório".* This is a weekly publication, which aims to create an open line of communication and broader collaboration between health professionals and national pharmacovigilance centre. In addition, this publication aims to inform health professionals and encourage them to be more aware about the events that can occur with the use of medicines and the importance of these events in improving the delivery of patient care.

3. Activity Description

3.1 Main Activity – National Pharmacovigilance System

During my internship I was responsible to "manage" the project of the national pharmacovigilance system (NPS), which comprised essentially in the management of the reports of suspected ADRs and quality problems received; the communication of any safety or quality alert and the sensitization of the health professional about the importance of pharmacovigilance in improving the delivery of healthcare to patients.

Despite the establishment, in 2006, by the DL 59/2006 that the marketing authorization holders (MAHs), physicians, technical directors of pharmacies and other health professionals should inform DGFM (now ARFA) of all adverse reactions that have knowledge, this legal requirement was not enough to awaken the responsibility in many of these professionals(28). Thus, to establish and define the main responsibilities of all key players in the pharmaceutical system, there is currently a proposal of a DL for the establishment of national pharmacovigilance system (NPS). This DL aims to define the rules of organization and functioning of this system, which is mainly based on the spontaneous reporting of ADRs and quality problems.

3.1.1 The project of the National Pharmacovigilance System

In Cape Verde, the diagnosis of pharmaceuticals sector produced under the NPP in 2003 identifies weaknesses in the medicines marketing authorization system, to which is added the large deficits in the monitoring of medicines during post-marketing. Thus, this instrument foresees in the field of pharmacovigilance "the establishment of a system for collecting and analysing data on adverse and toxic reactions arising from the use of medicines"(34). In line with the provisions in NPP appears in the DL nº 59/2006, which regulates the marketing authorization of medicines for human use, the determination that "*the DGFM while the pharmacovigilance system is not configured should receive reports of ADRs, analyse those information and propose measures deemed appropriate to protect public health"(28)*.

Nevertheless, with the competencies of market monitoring of medicines and pharmaceuticals assigned also to ARFA in the old status, the agency promoted the design of an integrated monitoring system - SIMFAR, supported by an information system that enables the implementation of a broad model of pharmacovigilance enabling timely

collection and processing of reports and management of signs and risk, both in terms of safety as in relation to quality problems which includes counterfeit medicines.

To this end, were initiated a series of meetings that had as its main objectives: the identification of shortcomings and their impact on the various players of the pharmaceutical sector; the discussion of the model more adequated to the current reality, as well as the awareness of the players to the importance of pharmacovigilance. Thus, of the recommendations worth mentioning the need and the urgency in the implementation of the pharmacovigilance system; the need to prepare a draft of the DL for the pharmacovigilance system, and the implementation of the decentralized scenario (with various national representations) as the most feasible for the pharmacovigilance system in Cape Verde.

Thus, of the decision to create the pharmacovigilance system in Cape Verde comes the option to start the process of preparing for integrating in the international program of drug monitoring, whose management is entrusted to the UMC. Nevertheless, Cape Verde should prepare and implement a plan of activities to comply with the minimum requirements set by the WHO. Hence, to this end, the ARFA promoted, along the Ministry of Health, the stage of awareness and advocacy for it to be designated as the authority to receive the functioning of the national centre of pharmacovigilance, and from the formal indication of ARFA as the national centre of pharmacovigilance, it was agreed with the UMC a work plan whose objectives included:

- Develop and implement a reporting system;
- Sensitize the health professionals about the importance of pharmacovigilance;
- Prepare for patients reporting;
- Establish a national commission of pharmacovigilance;
- Prepare for the transition from associate member to official member of the UMC international program;
- Submit to government approval the project of the NPS;

Of the realization of training in pharmacovigilance and the sensitization of the pharmacovigilance to the key players of the system, it is elaborated the proposal of the DL that institutes the NPS. The proposal predict a networking of various players such as authorities, inspection services, universities, public health institutions and other health professionals, which will be mainly based on spontaneous reporting of suspected ADRs and quality problems made by health professionals and patients. Thus, the NPS has as main objectives:

- Determine the methodologies for the collection, processing and dissemination of information on quality and safety of medicines;
- Identify and collect systematically suspected ADR's to medicines, quality problems and other issues related to the drug use;
- Analyse and evaluate the information collected on time, using support information systems and procedures;
- Identify signs and establish procedures for management and communication, in order to minimize the risks and maximize the benefits from the use of medicines;
- Systematically assess the profile of quality and safety of medicines used in the country; including the relationship between benefit and risk of medicines;
- Promoting rational use of medicines;
- Promote knowledge in pharmacovigilance;

The structure of the NPS integrates the following entities:

- **Central Organ of the NPS**

The Central Organ of the NPS is the national pharmacovigilance centre that works in ARFA, and is responsible for management and supervision of this system, adopting standards and technical guidelines that the pharmacovigilance activities must comply.

- **Risk Management Centres of regional or local scope**

Public health institutions that assume the role to collect validate and send reports of suspected ADR's and quality problems to the central organ of the NPS.

- **Delegates of pharmacovigilance (when appropriate)**

Health professionals both within and outside the National Health System (NHS) who are responsible for collecting reports of suspected ADR's and quality problems, and collaborate with the central organ of the NPS both in obtaining additional information for analysis and evaluation, and in the dissemination of safety measures decided by this body.

- **MAH and Economic Operators**

Establish pharmacovigilance procedures and nominate the technician in charge; collect and submit reports of suspected ADR's and quality problems to the central organ of the NPS; collaborate with the central organ of the NPS in the implementation of safety measures and assist in the dissemination of these.

- **Health professionals**

Professionals authorized to prescribe, dispense, and administer medications, or provide health care inside and outside the NHS, should communicate as soon as possible, to the central organ of the NPS, the risk management centre or the delegated of pharmacovigilance suspected ADR's or quality problems that have knowledge.

- **Health Educational Institutions and Consumer Representatives**

Constitute partners in the education of patients and the general public and in raising awareness about issues related to the safety and quality of medicines.

- **Pharmacovigilance Commission**

Constitute the advisory body of the NPS in pharmacovigilance issues, providing technical and scientific opinions relevant to the safety and quality of medicines, thereby contributing, to informed decisions by the central organ of the NPS. The competences of the pharmacovigilance commission include:

i. Assist scientifically and technically the NPS;
ii. Technical-scientific opinions;
iii. Prepare and approve its laws, and more submitted to it ;

The pharmacovigilance Commission will be constituted by a representative of the central organ of the NPS; a representative of DGFM; a representative of the National Health direction and a representative of the risk management centre. This proposal has already been submitted for government approval.

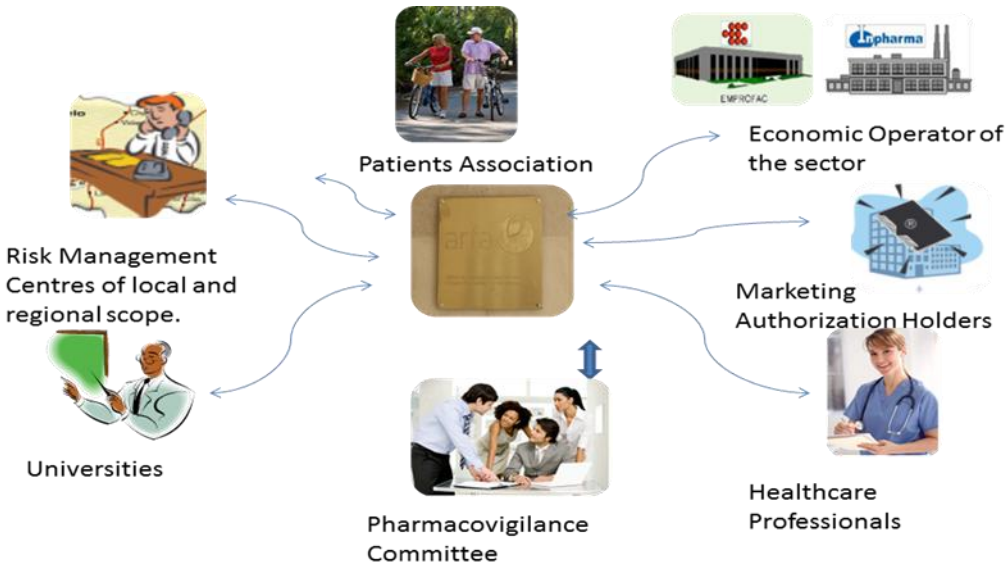

Figure 4: The NPS network

3.1.2 Spontaneous Reporting System

The main activity performed during this internship was to manage the reports of suspected of ADRs and quality problems.

In Cape Verde, the project of the NPS begins to receive its first reports in 2010, and since then the system relies on the spontaneous reports.

Spontaneous reporting is generally understood as an unsolicited communication by health care professionals or consumers that describes one or more suspected adverse events in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection scheme(40). The SRS plays a key role in the early detection of signals, allowing the generation of hypotheses concerning the possible adverse effects associated to the use of medicines. The added value of this system lies in that it allows experienced professionals in medicine safety monitoring to select reports that indicate the beginning of a serious ADR or one not detected earlier. Thus, the spontaneous report allows: early detection of ADR not yet identified; identification of risk groups; obtaining reliable estimates of toxicity compared between medicines within the same therapeutic class and continuous monitoring of safety data. Besides, it allows a monitoring on a large scale, covers the whole life cycle of the product and does not interfere with the prescribing habits(41).

Nevertheless, such as with other methods the SRS has important limitations to consider in the use of information from reports. Among the limitations import to highlight:(9)

- The recognition of the adverse effect

This recognition is subjective and imprecise, and although it is always assumed the existence of a causal relationship between the observed effect and the suspected medicine, all efforts are developed to exclude other possible explanation for the case.

- The underreporting

This is the major limitation of SRS. It is estimated that only 10% of all adverse reactions are reported(42).

- The bias

Unlike what happens with the data obtained in clinical trials, information resulting from spontaneous reporting is not controlled, being thus subject to the possible influence of several confounding factors.

- The quality of reporting

The ability to analyse the reports depends on the quality of information in the report made by health professionals.

In Cape Verde, the reports of suspected ADRs are accepted from health professionals, MAHs and patients (although they are not aware of that they can report). The reports can be sent by mail, fax or telephone, being on any means guaranteed the confidentiality of data in relation to the patient and the reporter(43). The reporting forms are designed to enable the collection of ADRs and quality problems related to medicinal product, and consist basically in eight topics, where four are considered mandatory. The eight topics comprise: the 1) identification of the patient, i.e., it's important to have an identified and identifiable patient; 2) the identification of the suspect product, which can include vaccine and other medicinal products; 3) the identification of concomitant medication 4) the description of the ADR or the quality problem; 5) the evaluation of the seriousness of the problem; 6) the evolution of the problem, i.e., in case of ADR, the patient's evolution in relation to the ADR; 7) the reports comments, where can be included medical history, drug allergy or other patient's habits that can have impact on the evaluation of the case; and last the 8) identification of the reporter. The current reporting form is identified below.

During this internship, one of the first activities that I have been proposed was to develop a new reporting form and abbreviated one (Appendix 1) since there was some missing information and how the information is requested does not allow much information to be gathered. For example, in the field "treatment of reaction," the idea of leaving the field blank to be filled by the profisisonal has not allowed that much information be obtained, and in a scenario in which the reporter had several options regarding the intervention made in relation to the suspected medicine, it would be more easy to obtain more information.

It lasted about one week to propose a new reporting form and an abbreviated one. For the abbreviated, the information considered essential were maintained and includes the information about the patients, the suspect product, the description of the problem and the reporter identification. At the end of the report form there is a clause that alert the health professional for the needs to provide more information of the case to the ARFA.

CENTRO NACIONAL DE FARMACOVIGILÂNCIA

Formulário de Notificação de Suspeitas de Reações Adversas e/ou Problemas Relacionados com Medicamentos

CONFIDENCIAL

Notificação nº:_____

Notificação de seguimento?_____ **Nº do processo precedente**_____

Os campos assinalados com (*) são de preenchimento obrigatório

1. Identificação do doente

*Nome ou iniciais:	*Sexo: F ☐ M ☐ Peso:_____Kg	*Data de nascimento ou idade:

2. *Medicamento/ Vacina Suspeito (a)

*Medicamento	*Dosagem	*Fabricante	Lote	Validade	*Inicio de uso	*Fim de uso	Razões de uso
					___/___/_____	___/___/_____	
					___/___/_____	___/___/_____	
					___/___/_____	___/___/_____	
					/___/_____	/___/_____	

3. Medicamentos concomitantes

Medicamento	Dosagem	Fabricante	Lote	Validade	Inicio de uso	Fim de uso	Razões de uso
					___/___/_____	___/___/_____	
					/___/_____	/___/_____	

4. *Descrição da Reação adversa ou problemas de qualidade *Data de inicio da reação: ____/____/_____

5. Gravidade

Morte☐	Risco de vida☐	Hospitalização prolongada☐	Assistência médica☐	Outro☐

Tratamento da reação:

6.Evolução

☐Recuperou, data____/____/_____ ☐Em Recuperação ☐Desconhecido

Sequelas: Sim☐ Não☐ Descrição da(s) sequela(s) _____

7. Comentários Adicionais (ex. histórico de saúde; alergias; exames médicos; etc.)

8. *Dados do Notificador

Nome:	**Profissão:**	**Contactos**
Endereço:	**Instituição:**	Telefone: Móvel: Email:
	Assinatura:	Data da Notificação: ___/____/_____

Obrigado pela sua colaboração em notificar!

Figure 5: The current report Form

The ADR reports are processed by the technician responsible for pharmacovigilance in ARFA, which during the internship was under my responsibility. The reports are processed using a method that involves three sequential steps comprising (Figure 6):

1. Reception and validation of reports;
2. Analysis and insertion on the database;
3. Feedback to the reporter;

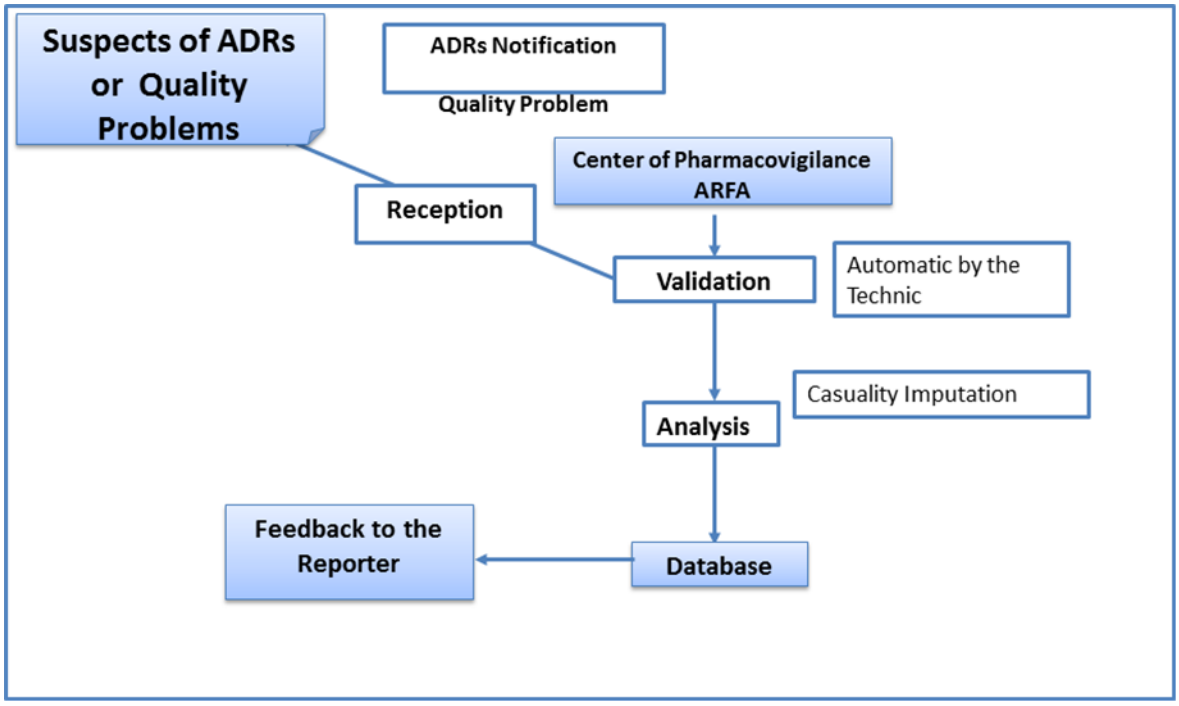

Figure 6: The Current Structure of the SRS

1. Reception and validation

A reporting of ADRs is related to a single case, where there is an identifiable patient and reporter, at least one suspected ADRs and at least one suspected drug. These are the minimum information required for the report to be inserted in the *VigiFlow* database, since the SIMFAR database is not working. For the reports to be considered valid it is required to contain the minimum information referred above. However, for any reports that do not present the minimum criteria, regardless if it is serious or unexpected, procedures are triggered to get immediately all the information needed from the reporter or other source available. If the initial reports are made orally or by telephone, procedures are triggered to obtain written confirmation by a health professional. The validation process consists essentially of data quality control.

2. Analysis and Insertion on the Database

The evaluation of each reports corresponds to the validation of information, determination of seriousness, predictability and performance of the procedure for imputation of causality, i.e., analyse whether the minimum criteria are present, if the reaction is serious or not, expected or unexpected and determine what is the probability of a causal relationship between the suspected ADR(s) and the suspect product, analysing also possible medicines interactions.

Since it essential to ensure that there is no misunderstanding in the data reported and to clarify questions about the verbatim it resorts to the latest versions of terminologies such as the WHO Drug Dictionary and WHO Adverse Reactions Terminology (WHO-ART) or Medical Dictionary for Regulatory Activities (MedDRA). The data collected in this phase and then entried in the database and coding can be used to future evaluation of any safety measures.

The seriousness of the adverse reaction is classified taking into account the judgment of the reporter, and when it does not provide, the classification is made considering the *List of Adverse Event / Reaction Terms to be Considered Always "Serious" published in Current Challenges in Pharmacovigilance: Pragmatic Approaches - Report of CIOMS Working Group V, Geneve, 2001, which is based on the WHO Critical Terms List.*

The classification of an adverse reaction as "expected" or "unexpected" is taken by resource to the Summary of Product Characteristics (SPC), and when the nature, intensity and evolution of the ADR reported does not differs from those described in the SPC, the reaction is classified as expected.

In terms of causality assessment, in Cape Verde all reports of ADRs received are assessed in terms of causality imputation. The causality assessment is part of the diagnostic process of ADR, which establish the relationship between a drug and a suspected reaction. The difficulty is to determine if a specific clinical condition was induced by a drug or not, since in practice, few adverse reactions are "certain" or "unlikely;" most are somewhere in between these extremes, i.e., "possible" or "probable." So, in the attempt to solve this problem, a variety of methods are used for causality assessment, each with its own advantages and limitations. These methods include:

- **Global Introspection:** causality inference obtained via clinical judgment, such as with an expert panel. This method is the most common approach for individual causality assessment of adverse drug reports. However the process of global introspection is known to be subjective, and despite its usefulness, the global

introspection method has been subject to criticisms of subjectivity, imprecision, and poor reproducibility because it is mainly based on expert clinical judgments.

- **Algorithms:** sets of specific questions with associated scores for calculating the likelihood of a cause-effect relationship. The use of a standardized instrument was intended to lead to a reliable and reproducible measurement of causality, in a structured way. There are several decision support algorithms available to make an explicit and reproducible assessment of causality. However, there is no universal algorithm, scoring can be arbitrary and responses to questions can be subjective.
- **Bayesian approaches:** express the relationship between the probability of a proposition before (prior estimate) and after the acquisition of the data (posterior estimate).

The three methods of causality assessments while different share common factors for consideration: the temporal relationship; dose relationship; de-challenge/re-challenge; recognized association with the product/class; pharmacological plausibility; underlying illness/concurrent conditions and other medications.

A variety of algorithms have been developed over these years, and some examples of algorithms/scales used include: WHO assessment scale; Karch and Lasagna's scale; Naranjo's scale; Kramer scale; Yale logarithm; European ABO system and the Spanish imputation system. The algorithm of Naranjo, Karch & Lasagna, and scale evaluation of the WHO are the most commonly used. In Cape Verde, the causality assessment methods used to analyze the reports are the algorithm approach (Naranjo's scale).

The algorithm of Karch & Lasagna consists of a number of closed questions to be answered in a dichotomous way. The combination of the results leads to the establishment of the "strength" of the causal relationship. However, although the method give objectivity to the diagnosis, it is useless to identify unknown reactions. Moreover, it does not provides criteria for individuals judgments or data for reproducibility evaluation, and an ADR can only be judged if there was re-exposure of the drug, which is rarely the case(44).

The Naranjo algorithm, or Adverse Drug Reaction Probability Scale, is a method of causality imputation by which it is assessed whether there is a causal relationship between an identified untoward adverse event and a drug by using a simple questionnaire to assign probability scores. This method consists of 10 questions that are answered as either Yes, No, or "Do not know", in which different point values (-1, 0, +1 or +2) are assigned to each answer. At the end a causality assessment is made by calculating the

number of points, and depending on the point score, the strength of a causal relationship is then considered such as definite, probable, possible or unlikely".

A simplified version of the 10 questions is provided in the table below(45).

Question	Yes	No	Do not know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
Are there alternative causes (other than the drug) that could solely have caused the reaction?	-1	+2	0
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar medicines in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0
Total score			
Total score categories are defined as follows: ADR is: certain > 9; probable 5-8; possible 1-4; unlikely 0.			

Table 1: Naranjo algorithm for assessing the causality of an ADR

Despite these limitations, these do not invalidate the proposed algorithms and their application within routine situations has been an important tool for the diagnosis and treatment of ADRs. Thus, considering the existence of limited human resources, the Naranjo's algorithm was chosen because it's less complex and less time consuming(46).

Thus, given the ineffectiveness of the SIMFAR database, the reports of ADRs are introduced since June 2011 in the *VigiFlow* database, in consequence of the integration of Cape Verde as member of the UMC.

The *VigiFlow* is an ICSR management system developed and hosted by UMC that is specially designed for use by national centers in the WHO programme for international drug monitoring. It is compatible with the ICH-E2B standard for electronic transmission of ICSRs. The ICSR data can be manually entered into *VigiFlow* with support from the terminologies such as the WHO Drug Dictionary and WHO-ART or MedDRA.

In the filling of the "report form" there are mandatory fields that must be completed for the case to be considered valid by the UMC and a built-in error check, which help the users to add data correctly. It is also possible to import ICSR data as XML files in the E2B format. In countries with several regional pharmacovigilance centers the access to the VigiFlow can be tailored to the respective rights(47). However, in Cape Verde there is one pharmacovigilance center, which is hosted at ARFA - the national pharmacovigilance center. There are several characteristics that make VigiFlow friendly to countries with limited resource as the case of Cape Verde, and such characteristics include (48):

- Handling of ICSRs

The possibility to add a digital "post-it" note to the ICSR makes communication easy in the VigiFlow. Once the report is complete and committed the first version of the ICSR is considered to be finalized. It is easy to retrieve reports to amend the contents or add follow-up information.

- Analysis

The availability of a search and statistics module in the VigiFlow makes easy to analyze the ICSR already inserted. The results can be exported in different output formats, either as PDF files or in spreadsheet format compatible with Microsoft Excel.

- Communication with External Organizations

The ICSR data can be sent to external contacts such as companies or other regulatory agencies either as PDF files (as computer files or hardcopy printouts) or in E2B formatted XML files.

- Technical Information

Since VigiFlow works over the internet, no local installations, back-ups or maintenance are necessary. The only requirements are a web browser, preferably Mozilla Firefox or

Internet Explorer, and an internet connection. The internet access is encrypted and any information stored in VigiFlow is only accessible by users within the same country/organization identified by their individual user name and password.

- Free of Charge

The UMC has available a version of VigiFlow with limited access, which is free of charge to member countries with limited resource. For this free version the functionality not available includes the E2B import and export and the search and statistics module. This version is primarily meant to be used for sending ICSRs to the UMC.

3. Feedback to the reports

After insertion of the report in the VigiFlow, is always sent a confirmation of receipt of the reporting to the reporter. The letter of feedback consists in a summary of the case, the identification number in the database and the causality attributed.

3.1.2.1 Risk Management and Communication

Due to its characteristic the SRS are the easiest to establish and the cheapest to run and have proven their value in identifying uncommon or unexpected ADRs and creating hypotheses to be tested in subsequent studies. Nevertheless, low and irregular spontaneous reporting rates greatly limit the advantages offered by this surveillance method, so it is difficult to determine the actual number of individuals experiencing an adverse reaction. So with this uncertainty and lack of information on the number of patients exposed to the drug in question, it is not possible to accurately estimate the rate and frequency of ADRs through spontaneous reporting. Furthermore, it is estimated that only 10% of all reported adverse reactions are reported(42, 49).

The identification and evaluation of signals constitute one of the main objectives of pharmacovigilance, and a signal is generally understood as “reported *information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously”*(49)*.* Generally it requires more than one report do generate a signal, depending on the seriousness of the event and the quality of information. The signals can arise through the SRS, prescription event monitoring, case controlled surveillance, record linkages, clinical trials databases and registries. Recent additions to these sources include large comprehensive population databases, such as electronic health-care records and health insurance systems.

In Cape Verde the SRS rely heavily on the spontaneous report. So, despite the annual number of notifications to be negative, the quality of reports sent by the reporters has

improved over those years. The quality of spontaneous reports is very important for the adequate assessment of the safety of medicine. For example, in 2010, total report received was 16, but only 8 reports had sufficient information to allow a proper analysis of the case and its inclusion in the database (Figure 7). The health professionals, especially pharmacists are those who most have reported over the years. The national distributor and producer or the MAHs do not report ADRs to the agency, despite the existence of the legal enforcement. Furthermore, local operators (industry and distributor) have no pharmacovigilance procedures installed.

	2010	2011	2012						
type of report	**total**	**total**	Jan	Mar	Jun	Sep	Oct	Nov	**total**
spontaneous	**8**	**4**	2	1	3	1	3	1	**11**

	2010	2011	2012						
type of sender	**total**	**total**	Jan	Mar	Jun	Sep	Oct	Nov	**total**
regulatory authority	**1**	**0**	2						**2**
health professional	**7**	**4**		1	3	1	3	1	**9**

Figure 7: Evolution of the Reporting of ADRs and quality problem

Thus, considering that the primary function of pharmacovigilance is to provide early alerts of unknown or previously incompletely documented ADRs ("Signs"), and the number of reports received so far, the generation of signal with SRS is almost nonexistent in Cape Verde.

Regarding the risk management, what I did during the internship, and is the current practice of ARFA, was daily visit the web site of medicines regulatory agencies of countries where medicines are most imported, namely the Infarmed website (Portugal), the ANVISA website (Brazil) and the European agency of medicine (EMA) website and search for any safety measure taken in respect to those medicines Figure 8

The safety information from external sources was used to enact regulatory measures. I was responsible for preparing any safety alert towards medicines available in the country, and send them to all health professionals in pharmacy, hospital, health center and private clinic. To quality problems with a specific batch, the alert is sent first to the national importer (EMPROFAC) to verify the existence of that specific batch and whether the batch is available, the alert is sent to hospital, pharmacies, health center and private clinic to proceed to the recalls.

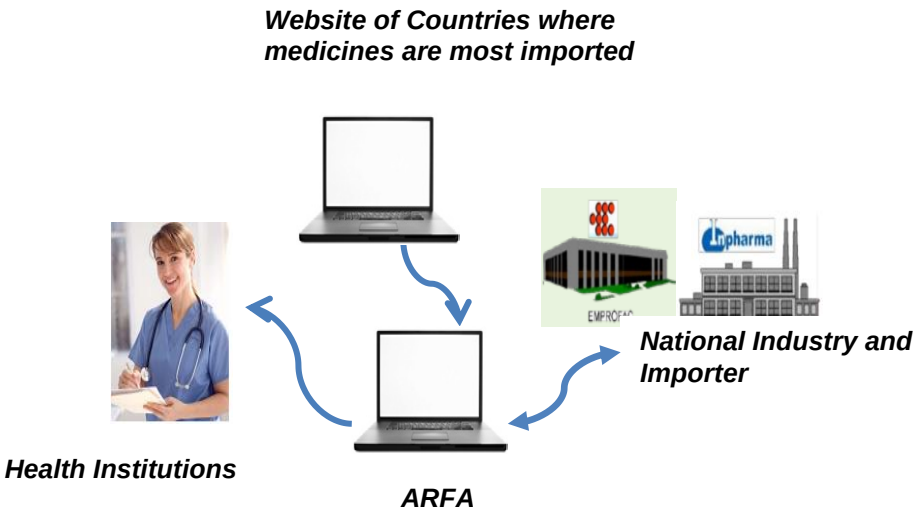

Figure 8: Safety measure cycle

For medicines produced locally, any external alert regarding the pharmacotherapeutic class that those medicines belongs are sent to the health professional, with the identification of those medicine produced locally. Annually the ARFA collect randomly samples of medicines available in the country, both imported and locally produce, and sent to the INFARMED to perform the laboratory analysis. Depending upon the results safety alert can be sent to the pharmacies, hospital, health centre and private clinic, in case of the medicine is already available in the market.

3.1.3 Educational Interventions on Pharmacovigilance

SRS is the most widely used method in the ADRs reporting, which is enables to early detect new, rare and serious ADRs. Spontaneous reports are generated during routine diagnostic appraisal of the patients by the health professional. However, substantial under-reporting exists and is the major obstacle for rapid and relevant signal detection of new and/or serious ADRs. Moreover knowledge, attitude, and practice regarding ADRs reporting has been studied extensively, and in general, lack of knowledge about ADRs and attitudes to ADRs are the major cause of under-reporting.

Improving reporting rates of ADRs is primarily about improving awareness of the need to report and the mechanisms used to submit the reporting form. Thus the degree to which health professional are informed about the principles of pharmacovigilance, and practice according to them, has a large impact on health care quality. Education and training of health professionals in medicine safety, by linking clinical experience of medicine safety with research and health policy, all serve to enhance effective patient care. Thus, the

dissemination of pharmacovigilance to healthcare professional and patients is paramount to improve the quality, safety and efficacy of medicines available.

However in the case of Cape Verde it cannot be talked now about the “underreporting” given that legally the system does not exist, and what can only be done is to sensitize the healthcare professional to this new concept and obligation in relation to the patient’s safety and the improvement of the health care delivered.

In relation to educational intervention the main activity performed during the training comprised:

- The preparation and training of healthcare professional of health structures, such pharmacies, hospitals and health centre for the importance of pharmacovigilance in improving patient’s safety;

Adverse reactions tend to be viewed, incorrectly, as “side effects” and thus are distracted from patients and doctors priorities, thus learning about the scope and severity of ADRs should start early in professional training. Moreover, good safety monitoring encourages health professionals to take fuller responsibility for the medicines they use. This improves clinical effectiveness and increases the confidence with which they and their patients use medicines.

Health professionals are more likely to identify and report important ADRs, if they have confidence in their ability to diagnose manage and prevent such reactions. National pharmacovigilance centres and training institutions play a central role in this by encouraging inclusion of the principles and methods of pharmacovigilance and the study of iatrogenic disease in the clinical practice and educational institutions.

The intended result of this training is to educate the health professionals in the area of ADRs /quality problems, and sensitizes them to the identification and reporting of any problem with medicines. Moreover, the construction of a surveillance system, supported by an information system, which allows the implementation of a comprehensive model of pharmacovigilance that allows timely the collection of reports of suspected ADRs and other problems related to medicines, their assessment, management and communication of risk, are of vital importance to the improvement of the quality of care delivery.

I was responsible to prepare the educational material and the training visit to the health centres and hospitals (Appendix 2). The training programs lasted about an hour and have as syllabus the:

- Worldwide importance of Pharmacovigilance;
- Methods used in Pharmacovigilance;

- National Pharmacovigilance System;
- Spontaneous Report System: The report form and other forms of reporting
- Case Studies in Pharmacovigilance

The program comprised primarily the north region of Santiago Island (Sta Catarina – health centre and the regional hospital, S. Miguel, S. Salvador do Mundo, Tarrafal, S. Lorenço dos orgãos). At the end of this educational program, approximately hundred eighty six health professional (understood as persons authorized to prescribe, dispense and administer medicines) were trained in how to report, what to report and with what urgency to report ADRs or quality problem to ARFA.

During this training session, the health professionals were distributed a simple questionnaire, which had as the general aims assess the knowledge of health professionals about issues relating to pharmacovigilance in Cape Verde in order to create a pharmacovigilance system efficient and adjusted to the current reality. The specific objectives of this questionnaire were to identify the causes of non-reporting and assess the percentage of health professionals who have already reported.

The questionnaire consisted into a theoretical and a practical part (see Appendix 3). The theoretical part consisted of questions about the definition of pharmacovigilance and its main purpose, as well about the knowledge of the existence of pharmacovigilance system in Cape Verde. The practical part consisted essentially in questions about the health professional attiudues before an ADR's, mainly the reasons for non-reporting. The question was constructed from a literature search of similar questionnaires (50, 51).

From a universe of hundred eighty (186) healthcare professional that assisted the training, ninety night (99) answered the questionnaire. The average age of the respondents was 37.72 years, being mostly females. Regarding the professional classes, about 28.3% of the respondents were nurses, 18.5% general practioners, 17.2% other health professionals (sanitary agent, psychologists), 15.2% technical assistants of pharmacy, 14.1% medical specialists and 6.5% pharmacists.

The analysis of the questionnaire indicated that only 20% of the respondents have already reported a ADRs or quality problems with medicine and that only 45% of the respondents known what pharmacovigilance is and its purpose. In addition, 35% of the respondents known about the existence of the reporting form and pharmacovigilance system in Cape Verde. In terms of main cause for non-reporting, lack of time (31.9%), indifference (31,9%) and financial incentives (29,8%) were the main reasons appointed by the respondents.

However, despite this preliminary conclusion achieved, it is important to highlight some shortcomings of this questionnaire. These shortcomings include, for example, the sample collected, which was a convenience sample, i.e, the sample was governed by the availability of the health professionals that attended to the training session, so the resulting sample is not representative of the general population. This method is a non-random sampling method, pragmatic and intuitive character. In terms of the questionnaire design it is important to stand out that there was no validation in relation to linguistic or interpretative issue and that no pilot study to assess the questionnaire's reproducibility were conducted.

- The preparation and distribution of weekly pharmacovigilance newspaper

One of the important strategies for integrating pharmacovigilance into clinical practice is to create open lines of communication and broader collaboration between health professionals and National Centre. For this to happen, the national pharmacovigilance centre needs to be situated in a two-way communication between health professional and the centre.

During the internship I was responsible to develop and implement this activity, which consists in the elaboration of pharmacovigilance bulletin. This newspaper is sent to the health professional in pharmacies, hospitals, health centre and private clinic. The main objective is to inform the health professional and encourage them to be more aware about the events that can appear with the use of medicines, and the significance of those events on the patient's safety and care provided. Each week the newspaper shows a different perspective of prescription, administration and dispense of medicine, both in relation to a specific medicine as in relation to a pharmacotherapeutic class. Example of this bulletin can be found in Appendix 4.

3.1.4 ADRs in Hospital Setting: Prospective Observational Cohort Studies

The main activity performed in relation to this study was to collaborate in the critical analysis of the project, the discussion of the sample sizing, the criteria to establish the suspected cases, the causality algorithm and the proposal of a formulary to collect data.

ADRs are encountered in as many as 10-20% of hospitalized patients and lead to 3–7% of all medical admissions(13). Drug-induced morbidity leads to increased suffering, prolongs hospital stay and causes a significant increase in hospital expenditure. Besides, aware that hospitals constitute an important element of post-marketing surveillance since

they concentrate cases of ADRs as a cause of hospitalization or its prolongation, it was proposed a study to obtain data, once non-existent, of the impact of ADRs in health service in Cape Verde.

The objectives of this project is to (1) initiate a process towards a reporting culture, raising awareness and encouraging health professionals to report, (2) obtain data on ADR's and quality problems occurring in the country and to characterize them and (3) to obtain comparison data between the intensive monitoring methodology and spontaneous report.

Thus, considering the lack of data of this nature in Cape Verde, the methodology proposed involve a comparative analysis of the data collected in the two central hospitals using different methodologies for reports collection: the hospital Agostinho Neto (Praia, Sotavento region) and the hospital Baptista de Sousa (Mindelo, Barlavento region). The intensive monitoring methodology will be used in Agostinho Neto Hospital after a pilot study in the Hospital Santa Rita Vieira to assess the sample size and testing of tools for information collection. A comparison will be made with data from spontaneous reports received from the same hospital and with the Hospital Baptista de Sousa.

Adverse drug reactions will be identified through intensive chart review, which is recognized as the gold standard for obtaining data on the incidence of ADRs(52). This intensive monitoring methodology will be used in the hospital Agostinho Neto and involves collection of information from medical records/ therapeutic records of suspected adverse reactions during the period required to identify the results. This study includes hospitalized patients in the two hospitals during the indicated period and excludes inpatient less than 24h. Thus, given the lack of previous studies, the sample size calculation will be done as a simple random sampling followed by stratification per service, and after the encryption the files will be randomly chosen.

The data that will be collected includes: patient demographics (age, gender), medication data (dosage, route of administration, frequency, start and end date of each prescription) and admission diagnosis. Data will be collected in a standardized format, for example, for prescribed medicines each chemical compound or combination compound according to the Anatomic Therapeutic Chemical (ATC) classification was considered, and for diagnose of disease the International Classification of Diseases version 10 (ICD10).

For each hospital involved, and if approved by the National Ethics Committee for Health Research (CNEPS), the protocol provides the:

- Presentation of the study to the Director for approval;
- Team-Composition with hospital staff to be appointed for that purpose;

- Development of protocols for confidentiality;
- Establish procedures and timeline for data collection;
- Training on pharmacovigilance: sessions on the importance of reporting in hospitals;
- Presentation of preliminary data by the researcher;

The investigator is required to guarantee the anonymity of patients referred in medical records, as well the confidentiality of all data.

Currently, the project has been already submitted to the CNEPS and the administrative board of the respective hospitals.

3.1.5 Risk Management Plan

The recognition that information about medicine safety is limited at the time of authorization only contributes to reinforce the need to implement measures to minimize identified and unidentified risk arising from the use of the medicines. Therefore, monitoring of medicines in the post-marketing is a tool of utmost importance to ensure the quality, efficacy and safety of consumers, thus helping to safeguard the public health. Moreover, as described in the report of the WHO *World Alliance for Patient Safety*, the skill and ability of programs to improve patient safety, depends on its ability to aggregate the most complete information on ADRs, so that they serve as a source of knowledge and basis for future preventive actions. The planning of pharmacovigilance activities necessary to characterize the safety profile of a medicines will only be improved if it is heavily based on the specific issues identified from the data generated during the pre-and post-market or based on pharmacological principles. The purpose of the identification and characterization of risk is to allow its minimization or mitigation whenever possible(53).

So, considering the news competences recently transferred to ARFA, which included the management of the medicines authorization system, I was proposed to develop a draft of the risk management plan (RMP).

The draft of the RMP developed aims to provide practical guidance for the preparation and elaboration of the RMP by the MAH or his representative, present in the national market. One of the legal requirements proposed is that the RMP should be submitted with the application for marketing authorization, without prejudice to be prompted for an update whenever there is a concern about a risk that could affect the risk-benefit ratio of the

medicine. The RMP should be submitted to all medicines, although in generic medicines, it is not necessary to include the clinical data.

The RMP consists of 6 modules, which are subdivided into parts, which include the summary of the product, the safety specification, pharmacovigilance plan, risk minimization plan, the references and the annexes. The general summary of the product provide the administrative information of the RMP, and a summary of general information (s) of product (s) that this plan covers. The safety specifications provide a synopsis of the safety profile of the product (s) and include(s) what is known or unknown about the product(s). Any security considerations should be discussed in this module as they constitute potential risks. The pharmacovigilance plan details the activities/studies which are intended to identify and/or characterize the safety concerns identified in safety specifications of the product (s). The risk minimization plan (RMP) must provide details of the measures to be undertaken to reduce the risks associated with a particular safety concern. The Annex will include the SPC, patient leaflet, the authorization status at a global level, as well as study programs or other relevant information.

3.2 Multidisciplinary Activity

During my internship I participated in other activities outside the main scope of my internship. Besides, one of the objectives of the internship was also to acquire multidisciplinary knowledge and experience. I performed several activities within the following area:

- Medicines Registration and Price Fixing
- Inspections to market operators

3.2.1 Medicines Registration and Price Fixing

During the internship I was responsible to register and calculate the price for over a thousand of medicines.

Under the NPP approved by Resolution n.º 16/2003, of 28 July, in which are absorbed the WHO guidelines, Cape Verde has recognized as priority issues for action in the pharmaceutical sector, the regulation of price of medicines and health products, the accessibility to quality medicines and the need for a monitoring system covering the pharmaceutical market. The priority in this regard is reinforced with the provisions of DL n. º 22/2009 and the DL n. º 64/2009 which establishes the legal regime to be met the criteria for pricing of medicines and establishes the SIMFAR(54).

The SIMFAR is a means of implementing the guidelines of the NPP, which aims to facilitate and /or ensure accessibility, by balancing the availability and the price, the quality of the medicinal product, the safety and effectiveness and rational use of medicines. The organizational structure of SIMFAR is based on technical and economic regulation, and includes:

- Marketing authorization
- Maximum price /prices monitoring and stocks;
- Post-marketing surveillance system (quality/safety).

This system provides the registration of all market operators. The registrations are made by completing of an electronic form. Furthermore, the manufacturer or importer must submit to ARFA an application for price approval, to which is assigned a unique medicine code to an unequivocal identification in the Cape Verdean market. The code is randomly assigned by the system and is related to a set of minimum information requirements.

Currently, the marketing authorization system is not working, and there are thousands of medicines available in the country that are not registered and do not have an

authorization. Thus, since this register system is not working as was provided, the ARFA is now requesting to the EMPROFAC information about those medicines, in order to register them in the SIMFAR's database.

During the registering of medicines, if the INN belongs to the NML in the same pharmaceutical form and dosage, it is attributed in the registering process the reimbursement echelon.

In Cape Verde, the reimbursement system is defined according to the beneficiaries, and there are essentially two regimes: the general and the special(55).

- General regime: For insured and their families the following echelon are applied: echelon A (85%), echelon B (75%), echelon C (55%) and echelon D (50%). Yet in the general regime are included pensioners and their families. This category includes only pensioners receiving pension equal to or greater than two and half times the national minimum wage (approximately 100€). For these beneficiaries the echelon to be applied is: echelon A (95%), echelon B (85%), echelon C (60%) and echelon D (55%).
- Special regime: This category includes pensioners and their families. This includes only pensioners receiving pension less than or equal to two and half times the national minimum wage. For these beneficiaries the medicines are 100 percent reimbursed.

Regarding the price, the ARFA is responsible for: a) approve the provisional prices and maximum prices of medicines covered by this regime b) authorize ordinary revisions, adjustments and extraordinary revisions and c) monitor and supervise its compliance.

In Cape Verde are subject to the pricing scheme all medicines in the country, except over-the-counter medicines, herbal remedies, homeopathic, handled or officinal prepared and veterinary medicines. The medicines excluded from the pricing system are, however, subject to the procedures provided for monitoring and regulation to be prepared by ARFA.

To the maximum price approved by ARFA is allowed to practice discounts throughout the medicine circuit, from the manufacturer to the pharmacy or to the consumer, since that safeguarded the quality of medicines, in particular as regards to shelf life. Moreover, the deductions made by pharmacies in reimbursed medicines by the INPS can focus exclusively on the part of the price not reimbursed.

For the purpose of pricing, medicines are classified in the following categories(35):

a) **Category I:** new medicines with therapeutic gain; new dosage forms of existing medicines in the market and new dosages involving new indication with therapeutic gain.

b) **Category II:** new medicines without therapeutic gain and new dosage forms of this medication;

c) **Category III:** medicines whose active substance already exists in the country, as well as new strengths and new presentations of existing medicines that do not involving new indication or therapeutic gain;

d) **Category IV:** generics medicines;

e) **Category V:** medicines used strictly in hospitals;

Medicines that cannot be fit into the above categories are provisionally classified in category II until completion of the revaluation and the subsequent classification in definitive category. Clinical data and other that demonstrate the existence of therapeutic gain in accordance with the guidelines established by the WHO are used in the final definition of the categories.

The prices of medicines sold in pharmacies are constituted by the Maximum Price to Pharmacy (MPP), and the Maximum Price to the consumer (MPC). The methodology used in calculating the MPP is based on comparison of the average of selling price to the wholesaler (SPW) of medicines identical or essentially similar in the countries set as reference, with the subsequent addition of marketing margin. The reference countries to be used in price comparison are Spain and Portugal.

For purposes of comparison the following criteria are considered in accordance with the following order of priority:

a) With the same pharmaceutical form, dosage and presentation;

b) With the same pharmaceutical form, dosage and closer presentation;

The MPP is determined based on the comparison between the prices of the nearest presentations in each reference countries. Where the difference between presentations and one whose price should be calculated is equidistant, is chosen the largest presentation. The criterion "presentation" for purposes of pricing applies up to three times the packaging of the medicines concerned. Whenever the package in question is more than three times the comparable medicine packaging, the pricing is determined by the administrative board of ARFA.

Thus, after comparison of the mean of SPW of medicines identical or essentially similar in the countries set as reference is added the corresponding margin, depending on the category in which the medicine is included. The marketing margin for the wholesaler to be used for purposes of determining the MPP for medicines included in categories I, II and III, and the medicines included in category IV, which the reference product is not sold in the

country is 24 percent for the lowest average of the SPW. For generic medicines with reference medicines[1] available in the country, the MPP should be 20 percent less than the reference medicine. The methodology used in calculating the maximum price of hospital medicines, enrolled in category V, is based on the comparison of the averages prices in reference countries, and the subsequent addition of the marketing margin of 15 percent.

The marketing margin of pharmacies and medicine sales points to be used for the purpose of MPC determination is:

a) 30 percent of the MPP for medicines in category I, II and III;´
b) 37.5 percent of the MPP for medicines in category IV;

For situation where the medicine is not being marketed in at least one of the reference countries, or the price was not found in the country of origin, and proven the urgency in terms of public health interest, the administrative Board of ARFA, heard the opinion of the Chairman of the National Medicines Commission, can fixing a provisional price until there are the conditions provided.

In Cape Verde, the prices of medicines are subject to annual review and adjustment prices, without prejudice to be made an especial review at any time, as determined by the Administrative Board of ARFA. Additionally, the manufacturer or importer can request for price adjustment.

To monitor the implementation of the price determined, the manufacturers, importers, distributors, wholesalers and pharmacies are required to submit to ARFA, each month, the data relating to the medicine marketing in respect to the previous month. Currently this requirement is fulfilled only by few of operators.

This methodology of price fixing is currently under revision, due to practical shortcomings, for example, there is a limited evaluation of the therapeutic gain of medicines, and the category II are seldom applied, due to limited information. Furthermore, the category IV is very broad to apply since all other medicine included in other category can have generic medicines. This category can only be applied for the first generic medicine that does not present any therapeutic gain. In addition, the sources of information on the price of imported medicines are very limited and insufficient.

[1] For the purposes of price fixing, the reference medicine is defined as the first medicine marketed in the country whose active substance has been authorized on the basis of full documentation.

3.2.2 Inspection

During the internship I was responsible to update the inspection checklist, the register form and prepare the inspection report (Appendix 5).

Routine Inspection

With the health sector reform, private pharmacies have become an important source of health care, frequently functioning as a first-line care. Thus, considering the representativeness of the private pharmacy, particularly in developing countries, and the fact that private provision of medicines has been associated with risks regarding availability, affordability, rational use and drug quality, he guarantee of an effective regulatory framework and permanent monitoring becomes therefore essential to ensure a balance between affordability and quality(56, 57).

In Cape Verde, the DL nº 34/2007 regulates the conditions of access to pharmaceutical activity and exercise in pharmacy. According to this DL the opening of a new pharmacy is preceded by a public tender, and the pharmacy can only open to the public after the attribution of the license by DGFM. The tender is open by order of the DGFM, whenever there are reasons for pharmaceutical coverage and heard the health center of the installation area, the ARFA and the consumers association, having jurisdiction in that county. The owner of a pharmacy can be individuals or commercial companies(58).

The pharmacy and medicine sale points are the only local authorized to sale medicines in Cape Verde. Moreover, the pharmacies can only supply medicines to the public present in NML and whose import has been specifically authorized. However, within the NML there are some medicines that the medicine sale point cannot sale, due to its characteristics.

The inspection activity is conducted in the scope of the annual visit to the operators of the pharmaceutical sector, called SIMFAR mission. The main objectives of the mission are to collect and update data from operators, to raise awareness among pharmacy professionals for the identification and reporting of suspected ADRs and quality problems, as well as verification of compliance in relation to the minimum requirements established by law. The expected result is to have professionals informed and aware about pharmacovigilance, as well as for the monitoring of aspects related to price, stock and medicines distribution.

The inspection consisted essential three phase:

- The update of the operator register

This consisted basically in collect general information about the pharmacy such the technical director, the address and contact, as well, listen constraints that pharmacies have been in relation to the EMPROFAC or other health structure.

- The sensitization of the importance of pharmacovigilance

This sensitization consisted essential in an introduction of what is pharmacovigilance, its importance in the improving of the quality of life of patients and health care. The sensitization also focused in what to report, how to report, and the urgency to report a suspected ADR and quality problem.

- The conformity verification;

The conformity assessment was conducted according to the decree-law 31/2007 which regulates the functioning of pharmacies, including requirements to be met by the facility pharmacies and medicine sales points.

The aspect checked during the visit was(59):

- ✓ Signalling: consist in verify if the word "Pharmacy" is correctly signed to the public, as well as information about operating period, the name of the technical director and the on-duty pharmacy.
- ✓ Documentation: according to the present DL a pharmacy should have a compilation of the main laws of the pharmaceuticals sector, as well as the license certificate available to the competent authorities.
- ✓ Facilities: the legislation also provides that pharmacies must have a minimum useful area of 80m², and it is also compulsory the existences of the following divisions: the area of public attendance, storage area, office, laboratory and /or attachment, toilet facilities and a ventilated area that allows to rest during the duty shift.
- ✓ Conditions of the divisions: according with the legislation in force the pharmacies should be kept in a permanent state of cleanliness and hygiene. For example, the medicine should be in places clean and fresh, not exposed to direct sunlight; properly arranged on the shelves, glazing cabinets, and away from the contact with the wall.
- ✓ Personals: The pharmacies should have at least the following personal: a technical director, and a technician pharmacy assistant. In addition, all workers should have the pharmacy bulletin of sanity updated, and should use white coats during the working period.

Following inspection, the pharmacies receive the inspection reports, which include the summary of the non-conformity found, as well as the corrective measures to be implemented. At the end of the internship I visited approximately 10 pharmacies.

Nevertheless, despite all the provisions, the applicable legislation is not being fully implemented, because due to the ineffectiveness of the medicine authorization system, the NML is not followed, and currently the pharmacies sold several medicines that were not authorized to be in the country and do not belong to the NML.

Inspection by anonymous tips

The involvement of the population in the pursuit of their right in have access to safe, effectives and quality medicines represent an add value in the medicine monitoring system. Thus, the improvement in the health service depends on the involvement of the whole community. In this line, often come to ARFA anonymous complaints that some unauthorized store is selling medicines. When those complaints comes to ARFA it is immediately initiated an inspection procedures.

During the internship, I had the opportunity to participate in an inspection to a Brazilian store that sold various herbal medicines, banned since 2005 in Brazil by ANVISA. Those medicines included: *Agonida, Depuratone, Acachofra Milian, Biotónico Fontoura, Composto para Varizes, Reumat Ervas, Ervas Vida, Tóniocardio, Saúde do Homem, Extrato concentrado Unha de gato, Glicos Ervas, Mulher Sempre Saudável* e *Relax Ervas.* It matter to highlight that in Cape Verde, regardless the type of medicines, for example OTC, herbal medicines, generic drug and innovator, the pharmacy and in drug sale point duly authorized are the only place authorized to sale medicines.

This has led to the instruction of an administrative offense, and in accordance with DL nº 34/2007 the sale of medicines in unauthorized stores constitutes offense punishable with a fine of € 50 and €1000 or €1500 and €3000 depending on whether the offender is a person or legal person.

Despite the evidence of growth of illegal market sale of medicines, the inspective capacity of ARFA is limited, and often the most seizures with medications in stores are made by the General Inspectorate of Economic Activities (IGAE).

4. Discussion

This chapter discusses the main gains achieved during this internship, the main difficulties encountered, as well as the general limitation of pharmacovigilance in Cape Verde.

Once this internship was held at the NMRA, it gave me the chance to understand how pharmaceutical sector in Cape Verde is organized and how marketing control and surveillance are performed in low-income country, such as the case of Cape Verde. Furthermore, since the pharmacovigilance is being installed, I had the opportunity to evaluate and comment the draft law for the creation of the national pharmacovigilance system.

During the internship it was not easy for me to realize that despite the global environment of increasing demands in terms of medicines safety, efficacy and quality, there are countries that have a poor control of the medicines available. For example, given that the medicine authorization system was not working, the ARFA often unknown what types and what medicines were available in the market.

One of the main difficulties encountered during this internship was the knowledge and availability of major legislation of the pharmaceutical sector, and the existence of overlapping competences between public entities. Nevertheless, I really appreciated the fact that I was entrusted with the responsibility of managing the pharmacovigilance of medicines through the promotion of new activities for this area. I was responsible to create and manage the pharmacovigilance bulletin, which aims to inform health professional about some pertinent issues of their clinical practice.

In Cape Verde, despite the remarkable progress in health indicators that the country reached, the current epidemiological transition, import dependence, the fragility of the authorization system of medicinal products, and evidence of growth of illegal market of medicines, are factors that evidences a need to strengthening the surveillance system. Thus, regarding the current pharmacovigilance practice, the main constraints are similar with the most African countries and can be broadly divided in:

- Policy, Law, and Regulation

Despite the DL that regulate the medicine authorization system have legal provisions that require MAHs, physicians, technical directors of pharmacies or other health professional to report all serious ADRs to the NMRA, this engagement is very limited. Thus, to address the inexistence of a national policy related to pharmacovigilance and medicine safety, there is a proposal currently under revision for being approved that establishes the NPS,

and consequently the MAH obligations in relation to each medicine available in the country.

- Signal Generation and Data Management

The scope of pharmacovigilance is limited in most of the African countries, and Cape Verde is no exception. Although there is a SRS in Cape Verde, the system mainly consists in data gathering. The pharmacovigilance database prospected is not currently in use due to some operational shortcomings and the reports are entered into the Vigiflow database.

- Risk Assessment and Evaluation

The reporting rate is minimal and generally less than 20 reports per million populations per year. Besides, the capacity to conduct medicine safety research exists, however yet active approaches to identify and evaluate medicine-related risks are limited. The incorporation of active surveillance activities into the NPS represent a viable alternative to improve the number of reports. Additionally, I have proposed a list of stimulus measures that can be adopted to increase the number of reports.

- Risk Management and Communication

It Cape Verde it is used the safety information from external sources (from other NMRA) to enact regulatory measures, although sporadically, which are sent to the health professional in form of alert or newsletter. Moreover, there are no procedures for managing or minimization of important known harmful effects of high-risk medicines. There is no formal requirement for risk management activity to prevent or minimize problems related to the medicine. To address this scenario, the ARFA should develop a framework, tools, and guidance documents for comprehensive risk management practices tailored to the current context. During the internship I was required to develop a proposal of the risk minimization and management plan for medicines of human use.

This scenario evidences that greater efforts are needed to build the pharmacovigilance system and to link existing activities to create a comprehensive pharmacovigilance system. The ARFA should develop strategic plans to incorporate both passive and active approaches, coordinate and work with all stakeholders, strengthen risk management and communication, and enhance the impact of pharmacovigilance and medicine safety systems. The successful execution of these plans will improve patient safety and health outcomes.

5. Conclusion

The 9-month experience earned during this internship was a unique experience, where I could put into practice the knowledge gained during the academic training which allowed me to provide pertinent contribution to ARFA. Besides, because of my multidisciplinary view and knowledge of the pharmaceutical European legislation, gained during the course, it makes me a great source of information and communication within the ARFA.

Nevertheless, I would like to highlight that several changes are taking place in the complex system of drug development, regulation and distribution, and the access to new essential medicines, such as artemisinin-based combination therapy and antiretroviral therapy in Africa, creates a greater need to monitor and promote safety and effectiveness of medicines. So, pharmacovigilance should be more proactive in monitoring their possible consequences.

To the Cape Verde pharmacovigilance system the strategic plan should go through efficient and timely identification, collection, assessment, and communication of medicine-related adverse events. Being in light that, a comprehensive system includes both active and passive surveillance methods, effective mechanisms to communicate medicine safety information to health care professionals and the public, collaboration among a wide range of partners and organizations, and incorporation of pharmacovigilance activities into the various levels of the health system.

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Appendix 1: Proposal for the New reporting Form and the Abbreviated Form

CENTRO NACIONAL DE FARMACOVIGILÂNCIA

CONFIDENCIAL

Formulario de notificação de suspeitas de Reações Adversas/Problemas de Qualidade para Profissionais de Saùde

Notificação nº:_____

Os campos assinalados com (*) são de preenchimento obrigatório

Suspeitas de Reações Adversas

1. *Identificação do doente

Nome (iniciais) _____ Sexo: F ☐ M ☐ Data de nascimento ou idade _____

Peso:_____Kg Altura:_____cm

2. *Produto Suspeito (se suspeita de interacção medicamentosa, considere os respectivos medicamentos como suspeitos)

*Medicamento (Nome comercial)	Lote	Posologia	Forma Farmacêutica	Inicio de uso	Fim de uso	Razão de uso
				___/___/___	___/___/___	
				___/___/___	___/___/___	

Que ação foi tomada?

☐ O medicamento foi suspenso devido à reação

☐ A dose do medicamento foi diminuida

☐ A dose do medicamento foi aumentada

☐ Nada foi alterado

No caso de ter suspenso a medicação, o medicamento foi reintroduzido?

☐ Sim ☐ Não ☐ Não sabe

3. Medicamentos concomitantes (inclui também automedicação e utilização de outros produtos)

Medicamento	Lote	Posologia	Forma Farmacêutica	Inicio de uso	Fim de uso	Razão de uso
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	
				___/___/___	___/___/___	

4. *Descrição da Reação adversa	***Data de inicio**	***Data de fim**	**Duração se a Reação for inferior a 1 dia**
	___/___/___	___/___/___	___h___min
	___/___/___	___/___/___	___h___min
	___/___/___	___/___/___	___h___min
	/ /	/ /	h min

Considera a(s) reação adversa (s) grave? Sim ☐ Não ☐

Se sim, porque considera grave?

☐ Resultou em Morte

☐ Colocou a vida em risco

☐ Motivou/Prolongou a Hospitalização

☐ Resultou em incapacidade

☐ Provocou anomalias congénitas

☐ Outro: _____

5. Tratamento/Evolução da Reação Adversa

Foi necessário efectuar algum tratamento da reação adversa?

☐ Não ☐ Sim Qual?_____

☐ Recuperou, data____/____/_____ ☐ Em Recuperação ☐ Desconhecido

Sequelas: Não ☐ Sim ☐ Qual? _____

6. Comentários (dados relevantes de história clínica, farmacológica, alergias e exames auxiliares de diagnóstico ou outros)

***Dados do Notificador** (campo de preenchimento obrigatorio tanto para reações adversas/problemas de qualidade)

Nome: _____ **Contatos:** **Email:** _____

Profissão: _____ **Tel:** _____

Instituição: _____ **Data:** ____/____/_____

Problemas de qualidade relacionados com Medicamentos

*Medicamento (Nome comercial): _____ Fabricante:_____

*N° de Lote: _____ Data de Validade do Medicamento: ____/____/_____

*Descrição do Problema:

Obrigado pela sua colaboração!

The Abbreviated Form

CENTRO NACIONAL DE FARMACOVIGILÂNCIA

Formulário Abreviado de Notificação de Suspeitas de Reações Adversas para Profissionais de Saúde

Notificação nº:_____

Confidencial

Os campos assinalados com (*) são de preenchimento obrigatório

A. *Identificação do doente

Nome (iniciais) _____ Sexo: F ☐ M ☐ Peso:_____Kg

Data de nascimento ou idade: _____

B. *Medicamento Suspeito (se suspeita de interacção medicamentosa, considere os respectivos medicamentos como suspeitos)

*Medicamento (Nome de Marca)	Razão de uso	Posologia	Forma Farmacêutica	Inicio de uso	Fim de uso

C. *Descrição da Reação adversa (RA)	**Data de inicio**	**Data de fim**	**Duração se for ≤ 1 dia**

Considera a(s) reação adversa (s) grave?

Sim ☐ Não ☐

Foi necessário efectuar algum tratamento da reação adversa?

☐Não ☐Sim Qual ?_____

D. Evolução

☐ Recuperou, data____/____/__ ☐ Em Recuperação ☐Desconhecido

Sequelas: Não ☐Sim ☐Qual? _____

E. *Dados do Notificador

Nome: _____ **Tel:** _____

Email: _____

Categoria Profissional: ☐Médico ☐Dentista ☐Farmacêutico ☐Enfermeiro

Instituição:

Assinatura:

Não esqueça que ao preencher este formulário abreviado compromete-se a disponibilizar mais informações à ARFA.

Obrigado pela sua colaboração!

Appendix 2: Pharmacovigilance Presentation

arfa

SISTEMA NACIONAL DE FARMACOVIGILÂNCIA EM CABO VERDE

Panorama Atual e Perspetivas Futuras

Tópicos a Abordar…

- Contexto Histórico
- Importância e Magnitude das Reações Adversas
- Panorama Atual de Cabo Verde
  - Etapas da criação do Sistema de Farmacovigilância
  - Anteprojecto do SNF
  - Métodos utilizados em Farmacovigilância
  - Sistema de Notificação Espontânea: Formulário
- Perspectivas Para o Sistema
- Caso Prático

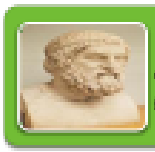
3

Contexto Histórico

" Ao submeter-se a um tratamento tens de ser muito saudável, porque para além de sua doença terás que suportar o medicamento."
Molière (1622-1673)

Reações Adversas Medicamentosa são conhecidas por serem tão antigas quanto o proprio medicamento em si...

4



Pensamento do épico Homero(± 950 a.C.)
"muito excelentes quando misturados, mas muito fatais"

Hipócrates (460 – 370 a.C
"primum non nocere"

Galeno (131-201)
"os medicamentos são capazes de provocar efeitos prejudiciais medios, fortes ou até mesmo fatais para o paciente, dependendo da dose dada"

Desastre de Talidomida

Talidomida (1957 – 1961)
- Hipnótico suave e profiláctico para enjoos matinais da gravidez
- 10 000 crianças com focomélia, por exposição intra-uterina

- ☑ **Consciencialização dos Profissionais de Saúde e do Público da importância das RAMs**
- ☑ **Regulamentação apropriada sobre Autorização de Comercialização**
- ☑ **Criação de Estruturas de Vigilância dos Medicamentos**

Pharmacovigilance / edited by Ronald D. Mann, Elizabeth Andrews. — 2nd ed.

Em consequência do desastre da Talidomida…

Em 1963: Farmacovigilância foi oficialmente criada

" Ciência e as atividades que se relacionam com a deteção, a avaliação, a compreensão e a prevenção dos acontecimentos adversos ou de qualquer problema que se relacione com o fármaco". OMS 2003

Nenhum medicamento está livre de riscos...

11

Reação Adversa Medicamentosa

Nenhum medicamento está livre de riscos...

12

Reação Adversa Medicamentosa (RAM)

- Qualquer resposta prejudicial e não desejada
- ocorre com doses habitualmente usadas para profilaxia, diagnóstico ou tratamento
- nexo de causalidade entre a ocorrência adversa e a utilização do medicamento." OMS

Fatores de Risco para RAMs

13

- Polimedicação
- Idade do doente
- Género
- Doenças de Base
- Raça e Polimorfismo Genético

Pharmacovigilance / edited by Ronald D. Mann, Elizabeth Andrews. — 2nd ed

Classificação das RAMs

14

- Tipo A (**A**umentado)

Aparecem dependendo das doses terapêuticas administradas, aumentando com o incremento das mesmas.

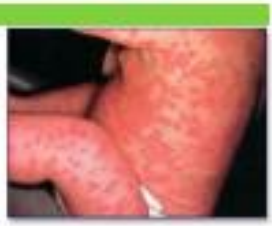
Ex: hemoragia por Varfarina

São geralmente previsíveis, dose-dependente e de baixa taxa de mortalidade

Pharmacovigilance / edited by Ronald D. Mann, Elizabeth Andrews. — 2nd ed

Classificação das RAMs

- Tipo B (**B**izarro)



Reações que não podem ser explicadas pela ação farmacológica do fármaco (idiossincráticas/imunológicas)

Ex: reação anafilática a penicilina

São geralmente imprevisíveis, independente da dose e de elevada taxa de mortalidade

Pharmacovigilance / edited by Ronald D. Mann, Elizabeth Andrews. — 2nd ed

RAMs constituem a principal causa de mortalidade e morbilidade nos cuidados de saúde…

- 3–7% de todas hospitalizações são devidos a RAMs;
- 10-20% dos pacientes hospitalizados sofrem de RAMs;
- RAMs estão entre a 4-6ª causa de morte nos EUA a frente da diabetes e de acidentes rodoviários;
- 197.000 mortos/ano na EU

Davies Emma (2007)Adverse Drug Reactions in Hospitals: A Narrative Review. Current Drug Safety

Sistema de Notificação Espontânea

Sistema de Notificação Espontânea

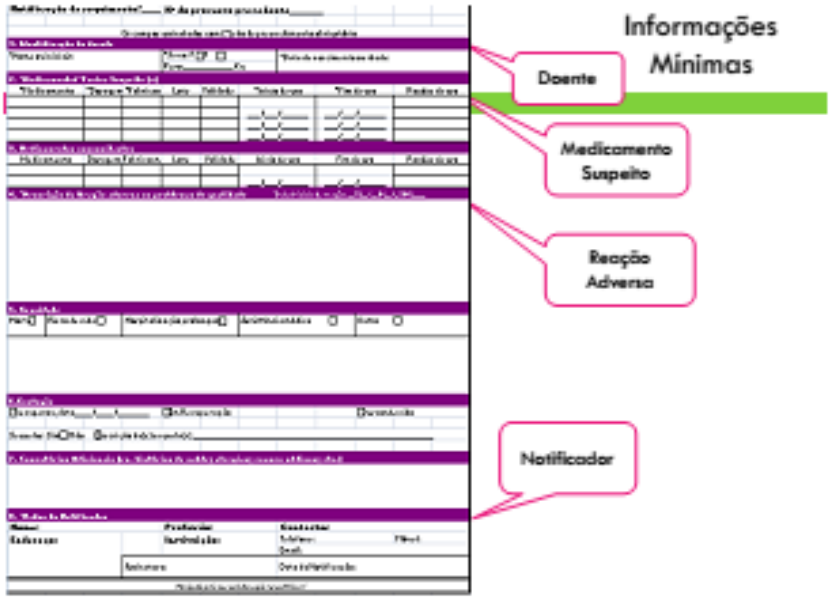
Como Notificar?

Formulários de Notificação

Tel.: 8002008

Fax: 262 49 70

Email:
vigimed@arfa.gov.cv



Sistema de Notificação Espontânea

28

O que Notificar?

Todas as <u>suspeitas</u> de RAMS em especial:

- RAM <u>Graves</u>
- RAM <u>Inesperadas</u>
- Ausência de Eficácia
- Interações Medicamentosas
- Problemas de Qualidade com Medicamentos

Sistema de Notificação Espontânea

39

RAM Graves

- Causa a Morte
- Põe a vida em perigo
- Motiva a hospitalização ou o seu prolongamento
- Conduz a incapacidade persistente ou significativa
- Causa anomalia congénita ou malformação

Sistema de Notificação Espontânea

40

RAM Inesperada

- Reação cuja natureza
- Gravidade
- Intensidade ou consequências
- Incompatíveis com os dados constantes do Resumo das Características do Medicamento (RCM)

Considerações Finais

- A monitorização pós-autorização contribui para garantir a qualidade, segurança e eficácia dos medicamentos, salvaguardando assim a saúde Pública.
- A eficácia do sistemas nacionais de farmacovigilância depende directamente da participação ativa de todos profissionais de saúde.

Não Hesite, NOTIFIQUE!

Questões ?

Caso Prático

Obrigado pela sua Atenção!!

ARFA- Agência de Regulação e Supervisão dos produtos Farmacêuticos e Alimentares
Achada Sto. António
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Praia – Cabo Verde
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Fax: + 238 262 49 70
Email: arfa@arfa.gov.cv

www.arfa.cv

Appendix 3: Questionnaire

QUESTIONÁRIO SOBRE O SISTEMA DE FARMACOVIGILÂNCIA EM CABO VERDE

Este questionário tem por objetivo avaliar o conhecimento dos profissionais de saúde sobre as questões relativas à farmacovigilância, de modo a criar um sistema de farmacovigilância eficiente e ajustado a realidade atual.

Por favor Preencha os seus dados demográficos:

Idade ☐ Sexo: ☐ M ☐F Qual a sua especialidade?_____

Qual é o serviço onde exerce funções?_____

Em que meio? ☐ Hospitalar ☐Centro de Saúde ☐Clinicas Privadas ☐Farmácias

Instruções: Selecione com um círculo a opção correta para cada uma das seguintes questões

1. Qual a definição de Farmacovigilância?
   a) Ciência que monitoriza a ocorrência de reações adversas medicamentosas nos hospitais
   b) Processo de melhoria da segurança dos medicamentos
   c) A ciência da deteção, avaliação, compreensão e prevenção dos efeitos adversos
   d) A ciência da deteção dos tipos e incidência de reações adversas após a comercialização do medicamento.

2. O principal propósito da farmacovigilância é
   a) Identificar a segurança dos medicamentos
   b) Calcular a incidência das reações adversas medicamentosas
   c) Identificar fatores de predisposição para as reações adversas medicamentosas
   d) Identificar reações adversas medicamentosas previamente desconhecidas

3. O centro internacional de monitorização das reações adversas medicamentosas está localizada nos/na
   a) Estados Unidos da América
   b) Austrália
   c) França
   d) Suécia

4. Tem conhecimento do sistema de notificações de suspeitas de reações adversas e problemas de qualidade em Cabo Verde?
   a) Sim
   b) Não

5. Em Cabo Verde qual é a entidade responsável pela monitorização de reações adversas e/ou problemas de qualidade a medicamentos?
   a) Direção Nacional de Saúde
   b) Serviço de Epidemiologia
   c) Direção Geral de Farmácia e do Medicamento (DGFM)

6. Identifiqueo (s) profissional (is) de saúde responsável pela notificação de reações adversas medicamentosas
   a) Médicos
   b) Farmacêuticos
   c) Enfermeiros
   d) Todos os indicados acima

7. Conhece o formulário de notificação?
   a) Sim
   b) Não

8. Em alguma ocasião, teve a intenção de notificar reações adversas medicamentosas e/ou problemas de qualidade e não dispunha do formulário?
   a) Sim
   b) Não

9. Aconteceu-lhe alguma vez suspeitar de uma reação adversa a um medicamento mas não chegar a preencher o formulário, mesmo dispondo dela?
   a) Sim
   b) Não

10. Alguma vez preencheu o formulário, que não chegou a enviar por causas distintas?
   a) Sim
   b) Não

11. Já alguma vez notificou uma suspeitas de reacções adversas e/ou problemas de qualidade?
   a) Sim
   b) Não

12. Quais de entre os seguintes fatores o (a) desencoraja de notificar suspeita de reações adversas/problemas de qualidade (escolha apenas uma)
   a) Falta de compensação económica para notificar
   b) Falta de tempo para notificar suspeita de reações adversas/problemas de qualidade
   c) Um único caso não notificado pode não afetar a base de dados de suspeita de reações adversas/problemas de qualidade

13. Acha que a notificação de suspeita de reações adversas/problemas de qualidade é uma obrigação do profissional de saúde?
   a) Sim
   b) Não
   c) Não Sabe
   d) Talvez

14. Já alguma vez leu algum artigo sobre a prevenção de reações adversas medicamentosas?
   a) Sim
   b) Não

15. Jáalguma vezrecebeu formação em como notificar uma suspeita de reações adversas medicamentosas/problemas de qualidade?
   a) Sim
   b) Não

Appendix 4: The Pharmacovigilance Bulletin

A Farmacovigilância, uma responsabilidade de Todos

Qualidade Eficácia Segurança

Observatório Farmacovigilância

Cada semana, um boletim destinado ao Profissional de Saúde

arfa

Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares

www.arfa.cv

N.º 001/ARFA-DRF/2013 22/03/13

Quem são os Utentes que mais sofrem Reações Adversas?

As reações adversas medicamentosas (RAMs) são consequências inseparáveis da ação do fármaco, podendo ser desencadeadas de modo previsível ou não. Assim sendo, dependendo da previsibilidade de tais reações, estas podem ser classificadas em dois grandes grupos: reações do tipo A e reações do tipo B.

As reações do tipo A são consideradas dose-dependentes, isto é, aparecem dependendo das doses terapêuticas administradas, aumentando com o incremento das mesmas. Estas reações são as mais comuns, geralmente previsíveis, dado que se encontram relacionados com a ação farmacológica do medicamento, e raramente são fatais.

Já as reações do tipo B são consideradas idiossincráticas/imunológicas, dado que o seu aparecimento não está relacionado com a ação farmacológica do medicamento. Estas são geralmente as menos comuns, embora estejam associadas a uma elevada taxa de mortalidade e morbilidade.

Vários são os fatores externos ao medicamento que contribuem para o surgimento das reações adversas, entre eles, podemos citar:

- Fatores intrínsecos ao doente: idade, sexo, caracteríscas genéticas que podem alterar a farmacocinética e farmacodinamia dos medicamentos.
- Fatores externos ao doente: ambiente, o grupo social, o médico e outros profissionais de saúde.

Estudos recentemente publicados sugerem que os indivíduos do sexo masculino com idade avançada e que vivem em áreas extremamente rurais são os que apresentam maiores taxas de morte por reações adversas. Na verdade, embora as reações adversas sejam um problema transversal a todas as faixas etárias, os idosos constituem um grupo de risco, dado que a maior parte deles se encontram polimedicados, apresentam doenças concomitantes e alterações nos parâmetros farmacocinéticos e farmacodinâmicos.

Ademais, os polimorfismos genéticos suscetíveis de afetarem os genes que codificam enzimas envolvidas no metabolismo dos fármacos podem representar um fator de risco importante para a ocorrência de reações adversas.

Notifique suspeitas de Reações Adversas a medicamentos através dos contatos: rgimed@arfa.cv Tel: 2626457- Fax: 2624970

Por exemplo, os doentes classificados como "metabolizadores lentos" têm maior propensão para acumular o medicamento no seu organismo, potenciando assim, a ocorrência das reações adversas. Nestes casos, o ajuste do medicamento para dose mais baixas constitui uma medida importante para minimizar o impacto de tais variações genéticas. Existem ainda os denominados "metabolizadores rápidos", que por sua vez necessitam de doses mais altas dos medicamentos, como consequência de estes serem excretados mais rapidamente do organismo.

Influência da Variabilidade Genética na Metabolização dos Medicamentos

Medicamentos	Gene	Fenótipo	Consequência
Diazepam	CYP2D6	Metabolizador Lento	Maior Sedação
Varfarina	CYP2C9	Metabolizador Lento	Hemorragia
Clopidogrel	CYP2C19	Metabolizador Rápido	Hemorragia
Dexametasona	CYP3A	Metabolizador Rápido	Arritmia
Candesartan	CYP2C9	Metabolizador Rápido	Hipertensão

A utilização destas informações na estratificação dos doentes, com a consequente adequação terapêutica, constituirá a título prospetivo, um poderoso instrumento para os prescritores e prestadores dos cuidados de saúde .

Referências:

Cohen N. Pharmacogenomics and Personalized. Humana Press, New Jersey, 2010
Aronson JK. Ed. Meyler's Side Effects of Drugs, 15th ed. Amesterdam, Elsevier, 2006
INFARMED. Farmacovigilância em Portugal, 2003
Shepherd G. et al, Adverse Drug Reaction Deaths Reported in United States. Vital Statistics, 2006

A notificação de qualquer suspeita de reação adversa é um contributo essencial para a monitorização contínua da segurança dos medicamentos.

Contamos com a sua colaboração!

Sabia que...

A dermatite de contacto alérgica é a reação adversa mais frequentemente descrita para os fármacos tópicos e os cosméticos. Entre alguns componentes de medicamentos tópicos implicados no desenvolvimento podemos citar: a bacitracina, neomicina, prometazina, difenidramina, benzocaína, procaína, corticosteróides, etc.

A Farmacovigilância, uma responsabilidade de Todos

Observatório de Farmacovigilância

Cada semana, um boletim destinado ao Profissional de Saúde

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Agência de Regulação e Supervisão dos Produtos Farmacêuticos e Alimentares

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N.º 004/ARFA-DRF/2013 16/04/13

Interações medicamentosas: como geri-las?

Dada a complexidade das combinações terapêuticas utilizadas atualmente, os conhecimentos especializados sobre os medicamentos representam hoje uma mais-valia para qualquer profissional de saúde no exercício das suas funções.

Reconhecidas há mais de 100 anos como consequências intrínsecas da ação farmacológica do medicamento, as **interações medicamentosas** são um problema comum durante o tratamento medicamentoso, resultando na maior parte das vezes, em reações adversas graves. Outrossim, a revisão da questão das interações medicamentosas e o seu impacto na saúde do doente torna-se premente na atual conjuntura.

A interação medicamentosa é tida como ocorrida quando a resposta de um paciente a um medicamento é alterada devido à presença de um outro medicamento, alimento, bebida, plantas medicinais ou agente químico ambiental. Os efeitos destas combinações podem ser:

- Sinérgicos ou aditivos;
- Antagónicos ou redutivos;
- Idiossincráticos ou tóxicos;

Os mecanismos geralmente envolvidos nas interações medicamentosas podem ser divididos em aqueles que têm por base a **farmacocinética** do medicamento e aqueles que têm por base a **farmacodinâmica**. As interações farmacocinéticas podem ocorrer durante um ou mais processos farmacocinéticos enquanto o medicamento atinge o seu local de ação, tais como durante a absorção, distribuição, metabolismo ou excreção. Estas reações podem resultar em alterações na concentração do medicamento no local de ação com a subsequente toxicidade ou diminuição da eficácia. Já as alterações farmacodinâmicas geralmente abarcam efeitos aditivos, sinérgicos ou antagónicos da ação do medicamento no mesmo recetor ou sistema fisiológico. São bastante comuns, embora não sejam facilmente reconhecidas.

Ademais, vários têm sido os fatores contributivos apontados para a ocorrência de tais reações, entres estas, os mecanismos de ação complexos dos novos agentes terapêuticos e a polifarmácia. Estudos recentemente publicados sugerem que o risco de reações adversas por interações medicamentosas **aumenta exponencialmente em pacientes que tomam mais de 4 medicações**, sendo a **população idosa** a classe mais comummente afetada.

Notifique suspeitas de Reações Adversas a Medicamentos: vigimed@arfa.cv Tel: 2626457 - Fax: 262 49 70

Além disso, estudos indicam que as interações medicamentosas são mais prováveis de resultar em consequências graves quando afetam idosos ou doentes gravemente debilitados.

As interações medicamentosas são consideradas um subconjunto das reações adversas, sendo responsáveis por 3-5% de todas as reações adversas medicamentosas. A compreensão de como ajustar a dose ou o regime de dosagem de um medicamento na presença de uma interação medicamentosa ou de como evitar tal interação pode melhorar significativamente o risco relativo do medicamento, e salvaguardar desta forma a segurança do doente.

Embora muitas reconhecidas interações medicamentosas são utilizadas para obter benefícios terapêuticos, o conhecimento do seus potenciais efeitos clínicos podem ser muitas vezes previstos com base na propriedade do medicamento, métodos de administração do medicamento e parâmetros específicos do doente.

Consequentemente, as reações adversas resultantes das interações medicamentosas podem ser prevenidas através de uma avaliação específica do paciente ou da situação em causa. Assim, a importância das interações medicamentosas prende-se essencialmente pelo seu caracter previsível, contribuindo assim, para a inserção de uma prática terapêutica segura e eficaz.

Medicamentos com interação	Efeito farmacológico	Alternativas
Amiodarona e Quinolonas (Levofloxacina)	Aumenta o risco de taxardas de pontas e/ou prolongamento da onda QT.	Alternativas antimicrobianas incluem Ciprofloxacina (risco relativo mais baixo), Penicilinas e Cefalosporina.
Carbamazepina e Macrólidos (Claritromicina e Eritromicina)	Aumenta a concentração da Carbamazepina e o risco de toxicidade.	Alternativas antimicrobianas incluem Azitromicina, Quinolonas e Cefalosporina de 2ª e 3ª geração. Se as alternativas não forem apropriadas monitorizar a concentração da Carbamazepina.
Cloridrozol e Omeprazol	Diminuição da concentração do cloridrozol com a consequente diminuição do efeito antiácido/antiácido.	Considerar um inibidor da bomba de protão como alternativa (excepto esomeprazol). Outras alternativas incluem bloqueadores do receptor H2 (excepto cimetidina).

Referências:

Bastel, C. et al. Drug Benefits and Risk. Uppsala Monitoring Center, IOS Press. 2ª Edition, 2008
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AMPS Pharmacology Expert. Adverse drug reaction and drug-drug interactions: consequence and cost. 2012
Dresser GK, Bailey DG. A basic conceptual and practical overview of interactions with highly prescribed drugs. Can J Clin Pharmacol. Winter 2002;9(4):191-198.

A notificação de qualquer suspeita de reação adversa é um contributo essencial para a monitorização contínua da segurança dos medicamentos.

Contamos com a sua colaboração!

Sabia que...

A Erva de São João ou Hipericão (Hypericum perforatum), quando utilizada em simultâneo com contraceptivos orais, pode resultar em hemorragia e perda da eficácia do contraceptivo.

Appendix 5: Inspection Materials

Verificação de Conformidade (De acordo com a portaria 31/ 2007 de 15 de Outubro)

Farmácia/PVM:		Data: ___/___/___		
	REQUISITOS	**Sim**	**Não**	**N/A**
1.	**Sinalização**			
	O nome da farmácia está devidamente assinalada ao público			
	O nome do diretor técnico está visível no interior e exterior da farmácia			
	O horário de funcionamento está de forma visível			
	A farmácia de serviço está afixada de forma visível			
2.	**Documentação**			
	Certificado de alvará			
	Compilação da Legislação farmacêutica			
	Livro de registo da movimentação de estupefacientes e psicotrópicos			
	Livro de reclamação e a sinalização da sua existência			
3.	**Área de atendimento ao Público**			
	Os medicamentos encontram-se:			
	a) Em lugares limpos e arejados			
	b) Não expostos à luz direta do sol			
	c) Devidamente arrumados nas prateleiras			
	d) Armários envidraçados			
	e) Afastados do contacto com a parede			
	f) Existência de produtos estranhos à profissão farmacêutica			
	Existência de armários com chave para estupefacientes e psicotrópicos			
4.	**Área de Armazenamento**			
	Recipientes destinados ao acondicionamento de medicamentos encontram-se:			
	a) Ordenadas			
	b) Rotuladas			
	c) Limpas			
	d) Não expostas ao público			
	e) Afastados do contacto com a parede			
5.	**Laboratório**			
	O laboratório/anexo obedece ao estipulado pela lei (luz própria, janela, chaminé, paredes revestidas de azulejo, nicho para eliminação de fumo e gazes)			
	Lavatório de louça vidrada ou de material inoxidável, pia e balde para recolha de água de lavagem dos pavimentos			
	Mesas de trabalho conforme o estipulado na lei			
6.	**Mobiliário e equipamentos**			
	Existência de frigorífico com termómetro			
	Armário – vestuário fechado para arrecadação de pertences dos funcionários			
7.	**Condições de Higiene**			
	Encontra-se em estado de asseio e higiene			
	Possui água corrente			
	Pessoal utiliza bata branca durante o funcionamento da farmácia			
	Todas as divisões estão cimentadas ou ladrilhadas, os tetos estucados			
8.	**Pessoal**			
	Diretor técnico			
	Técnico ou auxiliar de farmácia			

9.	**Área de Instalação Farmácia/PVM**			
	Área de atendimento ao público			
	Área de armazenamento			
	Escritório			
	Laboratório e/ou anexo			
	Instalações sanitárias			
	Área arejada que possibilite o descanso dos funcionários em serviço de turno			

OBSERVAÇÕES:

Inspector 1

_____

Inspector 2

_____

FICHA DE ATUALIZAÇÃO DE CADASTRO DE OPERADOR

1.	**Identificação da Farmácia/PVM**
	Nome:
	Endereço da sede:
	Telefone:
	Fax:
	Email:
	NIF:
	Nº de Licenças/Alvará:
2.	**Identificação do Gerente**
	Nome:
	Contato:
	Email:
	Profissão:
3.	**Identificação do Diretor Técnico**
	Nome:
	Contato:
	Email:
	Profissão:
4.	**Outros Funcionários (Nome/Profissão)**
	1.
	2.
	3.
	4.
5.	**Atividade**
	Data início de Atividade:
	Horário de Funcionamento:
6.	**Informatização**
	Acesso a Internet: Sim ☐ Não ☐
	Nível de conhecimento Informático(Diretor/Gerente): Bom ☐ Razoável ☐ Mau ☐
7.	**Desenvolvimento das Atividades**
	Requisição:
	a) Via fax ☐ Email ☐ Telefone ☐ Outros:
	b) Periodicidade:
	c) Valor Médio por requisição:
	Mercadoria:
	a) Período de Espera:
	b) Receção (ponto de levantamento):
	c) Procedimento de conferência da mercadoria:
	Transporte:
	a) Via Terrestre ☐ Marítima ☐ Aérea ☐
	b) Custo médio do transporte:
8.	**Constrangimentos**

RELATÓRIO DE VERIFICAÇÃO DE CONFORMIDADE

Âmbito

No âmbito das competências atribuídas à ARFA nos seus Estatutos e das grandes linhas de orientação da agência, foi concebido o Sistema Integrado de Monitorização do Mercado Farmacêutico (SIMFAR), cujo suporte legal e operacional permitem a recolha e tratamento de dados, sobre o fabrico, a importação, a distribuição, a comercialização e o consumo de medicamentos e produtos farmacêuticos. As informações recolhidas através deste sistema possibilitam realizar a monitorização do mercado farmacêutico, mais concretamente, no que respeita ao preço e stock, bem como a qualidade, segurança e eficácia dos medicamentos.

Assim, tendo em linha de conta a necessidade de recolher toda a informação de carácter quantitativo e qualitativo que possa servir de suporte para a implementação das diferentes áreas do SIMFAR, a direcção de regulação farmacêutica da ARFA, no âmbito das actividades programadas para o ano de 2013, levou a cabo uma visitajunto aos operadores do sector farmacêutico.

Objetivos

A missão teve como principaisobjetivos a recolha e actualizaçãodos dados dos operadores, a sensibilizaçãodos profissionais para a identificação e notificação de suspeitas de reações adversas á medicamentos e problemas de qualidade, bem como a verificação de conformidade da farmácia em relação as condições mínimas exigidas por lei.

Resultados Esperados

O resultado esperado é o de ter profissionais informados e sensibilizados para as questões de farmacovigilância, bem como para a monitorização dos aspectos relacionados ao preço, stock e distribuição de medicamentos.

Relatório

I - IDENTIFICAÇÃO DA FARMÁCIA/POSTO DE VENDA DE MEDICAMENTOS
Nome:
Endereço:
Telefone:
Email:
Nº de Licença/Alvará:
Número de profissionais do estabelecimento:
Horário de funcionamento: de _____ ás _____ horas
Nome/Contatodo Diretor Técnico:

II - CARACTERIZAÇÃO DA INSPEÇÃO
Data: _____/_____/_____ Horário: _____
Data da última inspecção:_____/_____/_____
i. Identificação das NãoConformidades
ii. *ContrangimentosApresentados*

III - CONSIDERAÇÕES

IV - EQUIPA*(Nome/Função)*

Em anexo: Ficha de verificação de conformidade.